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(54) Title: FLUORINATED ARYLAMIDE DERIVATIVES

(57) Abstract: The present invention relates to a novel class of fluorinated arylamide derivatives. The instant compounds can be used to treat cancer. The fluorinated arylamide derivatives can also inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The compounds of the invention may also be useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases. The present invention further provides pharmaceutical compositions comprising the hydroxamic acid derivatives and safe dosing regimens of these pharmaceutical compositions, which are easy to follow, and which result in a therapeutically effective amount of the hydroxamic acid derivatives in vivo.

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FLUORINATED ARYLAMIDE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to a novel class of fluorinated arylamide derivatives. The instant compounds can be used to treat cancer. The fluorinated arylamide compounds can also inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The compounds of the invention can also be useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases.

BACKGROUND OF THE INVENTION

The inhibition of HDACs can repress gene expression, including expression of genes related to tumor suppression. Inhibition of histone deacetylase can lead to the histone deacetylase-mediated transcriptional repression of tumor suppressor genes. For example, inhibition of histone deacetylase can provide a method for treating cancer, hematological disorders, such as hematopoiesis, and genetic related metabolic disorders. More specifically, transcriptional regulation is a major event in cell differentiation, proliferation, and apoptosis. There are several lines of evidence that histone acetylation and deacetylation are mechanisms by which transcriptional regulation in a cell is achieved (Grunstein, M., *Nature, 389*: 349-52 (1997)). These effects are thought to occur through changes in the structure of chromatin by altering the affinity of histone proteins for coiled DNA in the nucleosome. There are five types of histones that have been identified. Histones H2A, H2B, H3 and H4 are found in the nucleosome, and H1 is a linker located between nucleosomes. Each nucleosome contains two of each histone type within its core, except for H1, which is present singly in the outer portion of the nucleosome structure. It is believed that when the histone proteins are hypoacetylated, there is a greater affinity of the histone to the DNA phosphate backbone. This affinity causes DNA to be tightly bound to the histone and renders the DNA inaccessible to transcriptional regulatory elements and machinery.

The regulation of acetylated states occurs through the balance of activity between two enzyme complexes, histone acetyl transferase (HAT) and histone deacetylase (HDAC). The hypoacetylated state is thought to inhibit transcription of associated DNA. This hypoacetylated state is catalyzed by large multiprotein complexes that include HDAC enzymes. In particular, HDACs have been shown to catalyze the removal of acetyl groups from the chromatin core histones.

It has been shown in several instances that the disruption of HAT or HDAC activity is implicated in the development of a malignant phenotype. For instance, in acute promyelocytic leukemia, the oncoprotein produced by the fusion of PML and RAR alpha appears to suppress specific gene

transcription through the recruitment of HDACs (Lin, R.J. *et al.*, *Nature 391*:811-14 (1998)). In this manner, the neoplastic cell is unable to complete differentiation and leads to excess proliferation of the leukemic cell line.

U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511,990, the contents of which are hereby incorporated by reference, disclose hydroxamic acid derivatives useful for selectively inducing terminal differentiation, cell growth arrest or apoptosis of neoplastic cells. In addition to their biological activity as antitumor agents, these hydroxamic acid derivatives have recently been identified as useful for treating or preventing a wide variety of thioredoxin (TRX)-mediated diseases and conditions, such as inflammatory diseases, allergic diseases, autoimmune diseases, diseases associated with oxidative stress or diseases characterized by cellular hyperproliferation (U.S. Application No. 10/369,094, filed February 15, 2003, the entire content of which is hereby incorporated by reference). Further, these hydroxamic acid derivatives have been identified as useful for treating diseases of the central nervous system (CNS) such as neurodegenerative diseases and for treating brain cancer (See, U.S. Application No. 10/273,401, filed October 16, 2002, the entire content of which is hereby incorporated by reference).

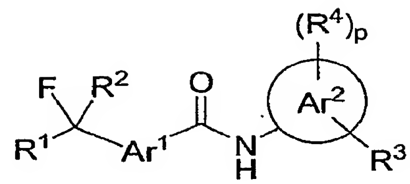
In view of the wide variety of applications for compounds containing hydroxamic acid moieties, the development of new HDAC inhibitors having improved properties, for example, increased potency or increased bioavailability is highly desirable.

SUMMARY OF THE INVENTION

The present invention relates to a novel class of fluoroalkylarylamide derivatives. The fluorinated arylamide compounds can be used to treat cancer. The instant amide compounds can also inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating a patient having a tumor characterized by proliferation of neoplastic cells. The compounds of the invention may also be useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases. The present invention further provides pharmaceutical compositions comprising the fluoroalkylarylamide derivatives, and safe, dosing regimens of these pharmaceutical compositions, which are easy to follow, and which result in a therapeutically effective amount of the fluoroalkylarylamide derivatives *in vivo*.

It has been unexpectedly discovered that certain fluorinated arylamide derivatives show improved activity as histone deacetylase (HDAC) inhibitors.

The present invention thus relates to compounds represented by Formula I and pharmaceutically acceptable salts, solvates and hydrates thereof, as detailed herein.



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The foregoing and other objects, features and advantages of the invention will be apparent from the following more particular description of the embodiments of the invention.

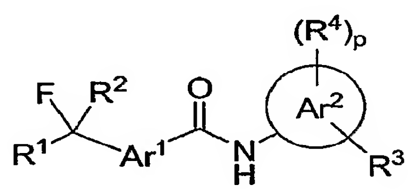
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a novel class of fluoroalkylarylamide derivatives. In one embodiment, the hydroxamic acid derivatives can inhibit histone deacetylase and are suitable for use in selectively inducing terminal differentiation, and arresting cell growth and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells. Thus, the compounds of the present invention are useful in treating cancer in a subject. The compounds of the invention may also be useful in the prevention and treatment of TRX-mediated diseases, such as autoimmune, allergic and inflammatory diseases, and in the prevention and/or treatment of diseases of the central nervous system (CNS), such as neurodegenerative diseases.

It has been unexpectedly and surprisingly discovered that certain fluoroalkylarylamide derivatives, show improved activity as histone deacetylase (HDAC) inhibitors.

COMPOUNDS

The present invention relates to compounds represented by Formula I:



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wherein:

Ar^1 is selected from: heteroaryl and aryl, wherein the aryl and heteroary 1 is optionally substituted with from 1 to 2 of R^6;

Ar^2 is a 5 to 6 membered heteroaryl or aryl;

R^1 is selected from: $R^5C(O)$-, aryl, heteroaryl and heterocyclic, wherein the aryl, heteroaryl and heterocyclic is optionally substituted with from 1 to 3 of the substituent R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9; or

R^1 and R^2 are combined to form -(CHR^9)$_u$- wherein one or more of the carbon atoms may be optionally replaced by a moiety selected from O, $S(O)_m$, -$N(R^{10})C(O)$-, and -NR^{11}-;

R^3 is OH, SH or NH_2;

R^4 is independently selected from hydrogen, OH, NH_2, nitro, CN, amide, carboxyl, C_1-C_7 alkoxy, C_1-C_7 alkyl, C_1-C_7 haloalkyl, C_1-C_7 haloalkyloxy, C_1-C_7 hydroxyalkyl, C_1-C_7 alkenyl, C_1-C_7 alkyl-C(=O)O-, C_1-C_7 alkyl-C(=O)-, C_1-C_7 alkynyl, halo group, amide, hydroxyalkoxy, -$NHSO_2$, -SO_2NH, C_1-C_7 alkyl-$NHSO_2$-, C_1-C_7 alkyl-SO_2NH-, C_1-C_7 alkylsulfonyl, C_1-C_7 alkylamino, di(C_1-C_7)alkylamino and L_2-R^8, wherein R^8 is heteroaryl, heterocyclic, aryl, or C_3-C_8 cycloalkyl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, C_1-C_4 alkylene, C_1-C_4 alkynyl, C_1-C_4 alkenyl, -O-, -S-, -N-, -C(=O)NH-, -NHC(=O)-, -NHC(=O)NH-, -SO_2NH-, -$NHSO_2$-, -SO_2-, -C(=O)- or -C(=O)O- ;

R^5 is selected from: amino, C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-$NHS(O)_2R$, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, aryl, heteroaryl and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino, N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and

heteroaryl), and sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

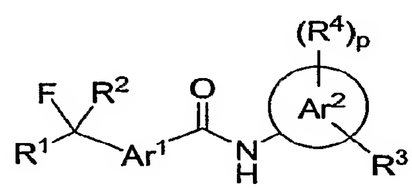
R^{10} is selected from: hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, heterocyclic, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^{11} is selected from: hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, heterocyclic and -C(O)-R (where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl),wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

p is 1, 2, 3 or 4;
u is 3, 4 or 5;

or a stereoisomer or pharmaceutically acceptable salt thereof.

In an embodiment, the compounds of the instant invention are represented by Formula I:



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wherein:

Ar^1 is selected from: heteroaryl and aryl, wherein the aryl and heteroary l is optionally substituted with from 1 to 2 of R^6;
Ar^2 is a 5 to 6 membered heteroaryl or aryl;

R^1 is selected from: R^5C(O)- and [1,3,4]oxadiazol-2-yl, wherein the [1,3,4]oxadiazol-2-yl is optionally substituted with R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is OH, SH or NH_2;

R^4 is independently selected from hydrogen, OH, NH_2, nitro, CN, amide, carboxyl, C_1-C_7 alkoxy, C_1-C_7 alkyl, C_1-C_7 haloalkyl, C_1-C_7 haloalkyloxy, C_1-C_7 hydroxyalkyl, C_1-C_7 alkenyl, C_1-C_7 alkyl-C(=O)O-, C_1-C_7 alkyl-C(=O)-, C_1-C_7 alkynyl, halo group, amide, hydroxyalkoxy, -$NHSO_2$, -SO_2NH, C_1-C_7 alkyl-$NHSO_2$-, C_1-C_7 alkyl-SO_2NH-, C_1-C_7 alkylsulfonyl, C_1-C_7 alkylamino or di(C_1-C_7)alkylamino or L_2-R^8, wherein R^8 is heteroaryl, heterocyclic, aryl, or C_3-C_8 cycloalkyl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, C_1-C_4 alkylene, C_1-C_4 alkynyl, C_1-C_4 alkenyl, -O-, -S-, -N-, -C(=O)NH-, -NHC(=O)-, -NHC(=O)NH-, -SO_2NH-, -$NHSO_2$-, -SO_2-, -C(=O)- or -C(=O)O- ;

R^5 is selected from: amino, C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

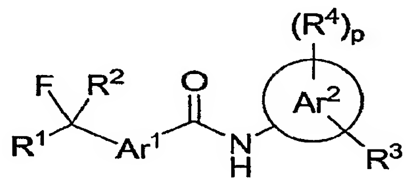
R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)2R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, aryl, heteroaryl and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)2R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

p is 1, 2, 3 or 4;
or a stereoisomer or pharmaceutically acceptable salt thereof.

The present invention also relates to compounds represented by Formula I:



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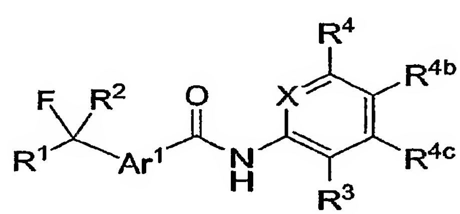
wherein:

Ar^2 is selected from phenyl, pyridyl, thienyl, pyrazolyl and pyrrolyl;

R^2 is selected from hydrogen, C_1-C_6 alkyl, fluoro and aryl, wherein the alkyl and aryl are optionally substituted with from 1 to 3 of the substituent R^9;
R^3 is NH_2;
and the remaining substituents and variables are as described above for the compounds of Formula I;

or a stereoisomer or pharmaceutically acceptable salt thereof.

The present invention further relates to compounds represented by Formula II:



II

wherein:
Ar^1 is selected from: heteroaryl and aryl;
X is CR^{4a} or N;

R^1 is selected from: $R^5C(O)$- and [1,3,4]oxadiazol-2-yl, wherein the [1,3,4]oxadiazol-2-yl is optionally substituted with R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is OH, SH or NH_2;

R^4 is selected from hydrogen, C_1-C_7 alkyl and L_2-R^8, wherein R^8 is heteroaryl or aryl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, and C_1-C_4 alkylene;

R^{4a}, R^{4b} and R^{4c}, are independently selected from hydrogen and fluoro;

R^5 is selected from: C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

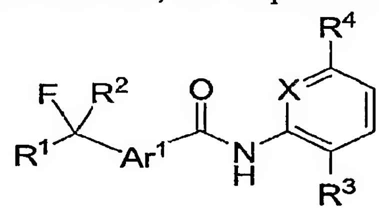
R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

or a stereoisomer or pharmaceutically acceptable salt thereof.

In an embodiment of the instant invention, the compounds are represented by Formula III:



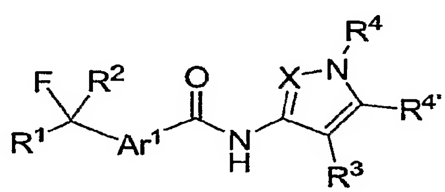
III

X is CH;

R^2 is selected from hydrogen, C_1-C_6 alkyl, fluoro and aryl, wherein the alkyl and aryl are optionally substituted with from 1 to 3 of the substituent R^9;
R^3 is NH_2;
and the remaining substituents and variables are as described above for the compounds of Formula II;

or a stereoisomer or pharmaceutically acceptable salt thereof.

The present invention further relates to compounds represented by Formula IV:



IV

wherein:
Ar^1 is selected from: heteroaryl and aryl;
X is CH or N;

R^1 is selected from: $R^5C(O)$- and [1,3,4]oxadiazol-2-yl, wherein the [1,3,4]oxadiazol-2-yl is optionally substituted with R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is OH, SH or NH_2;

R^4 is selected from hydrogen, C_1-C_7 alkyl and L_2-R^8, wherein R^8 is heteroaryl or aryl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, and C_1-C_4 alkylene;

$R^{4'}$ is selected from hydrogen and fluoro;

R^5 is selected from: C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

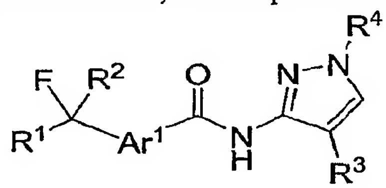
R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino, N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), and sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

$R^{4'}$ is selected from hydrogen and fluoro;

or a stereoisomer or pharmaceutically acceptable salt thereof.

In an embodiment of the instant invention, the compounds are represented by Formula V:



V

R^2 is selected from hydrogen, C_1-C_6 alkyl, fluoro and aryl, wherein the alkyl and aryl are optionally substituted with from 1 to 3 of the substituent R^9;
R^3 is NH_2;
and the remaining substituents and variables are as described above for the compounds of Formula III;

or a stereoisomer or pharmaceutically acceptable salt thereof.

Specific examples of the compounds of the instant invention include:

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Fluoro-phenylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(4-Chloro-phenylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-{[1-(*S*)-(4-Chloro-phenyl)-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(2,4-Dichloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Fluoro-methylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(4-Amino-biphenyl-3-ylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(2,2-Difluoro-1-phenyl-ethylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-{[1-(*R*)-(4-Chloro-phenyl)-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[Fluoro-(indan-1-(*S*)-ylcarbamoyl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-{[1-(*S*)-Phenyl-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Fluoro-methylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-[Fluoro-(1-(*S*)-phenyl-ethylcarbamoyl)-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-[(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide;

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-{Fluoro-[(pyridin-3-ylmethyl)-carbamoyl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

N-(4-amino-1-phenyl-1H-pyrazol-3-yl)-6-[2-(benzylamino)-1-fluoro-2-oxoethyl]-1-benzothiophene-2-carboxamide;

6-[Fluoro-(5-methyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-{Fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-[Fluoro-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-(Diethylcarbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Carbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Diethylcarbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-fluoro-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(dimethylcarbamoyl-fluoro-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(fluoro-isopropylcarbamoyl-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-oxo-2-pyrrolidin-1-yl-ethyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(ethylcarbamoyl-fluoro-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(fluoro-methylcarbamoyl-methyl)-benzamide;

[4-(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-phenyl]-fluoro-acetic acid methyl ester;

[4-(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-phenyl]-fluoro-acetic acid;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[1-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-oxo-2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-morpholin-4-yl-2-oxo-ethyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[2-(3-dimethylamino-pyrrolidin-1-yl)-1-fluoro-2-oxo-ethyl]-benzamide;

N-(2-Amino-5-thiophen-3-yl-phenyl)-4-(carbamoyl-fluoro-methyl)-benzamide;

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-[(3-cyano-phenylcarbamoyl)-fluoro-methyl]-benzamide;

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide;

N-(4-Amino-5-fluoro-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(difluoro-methylcarbamoyl-methyl)-benzamide;

N-(4-amino-1-phenyl-1*H*-pyrazol-3-yl)-4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzamide;

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{difluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-1-methylcarbamoyl-ethyl)-benzamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Other specific examples of the compounds of the instant invention include:

6-{[1-(*S*)-Phenyl-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide; TFA salt;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide; TFA salt;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide; TFA salt;

6-{Fluoro-[(pyridin-3-ylmethyl)-carbamoyl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide; HCl salt; and

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide; TFA salt.

Other specific examples of the compounds of the instant invention include:

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-((*S*)-fluoro-methylcarbamoyl-methyl)-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-((*R*)-fluoro-methylcarbamoyl-methyl)-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[(1*R*)-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[(1*S*)-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-(*S*)-fluoro-methyl)-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-(*R*)-fluoro-methyl)-benzamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

Chemical Definitions

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, C_1-C_{10}, as in "C_1-C_{10} alkyl" is defined to include groups having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbons in a linear or branched arrangement. For example, "C_1-C_{10} alkyl" specifically includes methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *i*-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, and so on. The term "cycloalkyl" means a monocyclic saturated aliphatic hydrocarbon group having the specified number of carbon atoms. For example, "cycloalkyl" includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, and so on. In an embodiment of the invention the term "cycloalkyl" includes the groups described immediately above and further includes monocyclic unsaturated aliphatic hydrocarbon groups. For example, "cycloalkyl" as defined in this embodiment includes cyclopropyl, methyl-cyclopropyl, 2,2-dimethyl-cyclobutyl, 2-ethyl-cyclopentyl, cyclohexyl, cyclopentenyl, cyclobutenyl and so on. In an embodiment, if the number of carbon atoms is not specified, "alkyl" refers to C_1-C_{12} alkyl and in a further embodiment, "alkyl" refers to C_1-C_6 alkyl. In an embodiment, if the number of carbon atoms is not specified, "cycloalkyl" refers to C_3-C_{10} cycloalkyl and in a further embodiment, "cycloalkyl" refers to C_3-C_7 cycloalkyl. In an embodiment, examples of "alkyl" include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl and *i*-butyl.

The term "alkylene" means a hydrocarbon diradical group having the specified number of carbon atoms. For example, "alkylene" includes - CH_2-, -CH_2CH_2- and the like. In an embodiment, if the number of carbon atoms is not specified, "alkylene" refers to C_1-C_{12} alkylene and in a further embodiment, "alkylene" refers to C_1-C_6 alkylene.

When used in the phrases "alkylaryl", "alkylcycloalkyl" and "alkylheterocyclyl" the term "alkyl" refers to the alkyl portion of the moiety and does not describe the number of atoms in the aryl and heteroaryl portion of the moiety. In an embodiment, if the number of carbon atoms is not specified, "alkyl" of "alkylaryl", "alkylcycloalkyl" and "alkylheterocyclyl" refers to C_1-C_{12} alkyl and in a further embodiment, refers to C_1-C_6 alkyl.

If no number of carbon atoms is specified, the term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferably one carbon to carbon double bond is present, and up to four non-aromatic carbon-carbon double bonds may be present. Thus, "C_2-C_6 alkenyl" means an alkenyl radical having from 2 to 6 carbon atoms. Alkenyl groups include ethenyl, propenyl, butenyl, 2-methylbutenyl and cyclohexenyl. The straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated.

The term "alkynyl" refers to a hydrocarbon radical straight, branched or cyclic, containing from 2 to 10 carbon atoms and at least one carbon to carbon triple bond. Up to three carbon-carbon triple bonds may be present. Thus, "C_2-C_6 alkynyl" means an alkynyl radical having from 2 to 6 carbon atoms. Alkynyl groups include ethynyl, propynyl, butynyl, 3-methylbutynyl and so on. The

straight, branched or cyclic portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated.

In certain instances, substituents may be defined with a range of carbons that includes zero, such as (C_0-C_6)alkylene-aryl. If aryl is taken to be phenyl, this definition would include phenyl itself as well as -CH_2Ph, -CH_2CH_2Ph, $CH(CH_3)CH_2CH(CH_3)$Ph, and so on.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 atoms in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl and biphenyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment can be via the aromatic ring or non-aromatic ring.

In another embodiment, "aryl" is an aromatic ring of 5 to 14 carbons atoms, and includes a carbocyclic aromatic group fused with a 5-or 6-membered cycloalkyl group such as indan. Examples of carbocyclic aromatic groups include, but are not limited to, phenyl, naphthyl, e.g., 1-naphthyl and 2-naphthyl; anthracenyl, e.g., 1-anthracenyl, 2-anthracenyl; phenanthrenyl; fluorenonyl, e.g., 9-fluorenonyl, indanyl and the like. A carbocyclic aromatic group is optionally substituted with a designated number of substituents, described below.

The term heteroaryl, as used herein, represents a stable monocyclic, bicyclic or tricyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. In another embodiment, the term heteroaryl refers to a monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, or S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment can be via the aromatic ring, the non-aromatic ring or via the heteroatom containing ring, respectively.

In another embodiment, "heteroaryl" is a monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, or S. Examples of heteroaryl include, but are not limited to pyridyl, e.g., 2-pyridyl (also referred to as α-pyridyl), 3-pyridyl (also referred to as β-pyridyl) and 4-pyridyl (also referred to as (γ-pyridyl); thienyl, e.g., 2-thienyl and 3-thienyl; furanyl, e.g., 2-furanyl and 3-furanyl; pyrimidyl, e.g., 2-pyrimidyl and 4-pyrimidyl; imidazolyl, e.g., 2-imidazolyl; pyranyl, e.g., 2-pyranyl and 3-pyranyl; pyrazolyl, e.g., 4-pyrazolyl and 5-pyrazolyl; thiazolyl, e.g., 2-thiazolyl, 4-thiazolyl and 5-thiazolyl; thiadiazolyl; isothiazolyl; oxazolyl, e.g., 2-oxazoyl, 4-oxazoyl and 5-oxazoyl; isoxazoyl; pyrrolyl; pyridazinyl; pyrazinyl and the like. Heterocyclic aromatic (or heteroaryl) as defined above may be optionally substituted with a designated number of substituents, as described below for aromatic groups.

In an embodiment, "heteroaryl" may also include a "fused polycyclic aromatic", which is a heteroaryl fused with one or more other heteroaryl or nonaromatic heterocyclic ring. Examples include, quinolinyl and isoquinolinyl, e.g., 2-quinolinyl, 3-quinolinyl, 4- quinolinyl, 5-quinolinyl, 6-quinolinyl, 7-quinolinyl and 8-quinolinyl, 1-isoquinolinyl, 3-quinolinyl, 4-isoquinolinyl, 5-isoquinolinyl, 6-isoquinolinyl, 7-isoquinolinyl and 8-isoquinolinyl; benzofuranyl, e.g., 2-benzofuranyl and 3-benzofuranyl; dibenzofuranyl, e.g., 2,3-dihydrobenzofuranyl; dibenzothiophenyl; benzothienyl, e.g., 2-benzothienyl and 3-benzothienyl; indolyl, e.g., 2-indolyl and 3-indolyl; benzothiazolyl, e.g., 2-benzothiazolyl; benzooxazolyl, e.g., 2-benzooxazolyl; benzimidazolyl, e.g., 2-benzoimidazolyl; isoindolyl, e.g., 1-isoindolyl and 3-isoindolyl; benzotriazolyl; purinyl; thianaphthenyl, pyrazinyland the like. Fused polycyclic aromatic ring systems may optionally be substituted with a designated number of substituents, as described herein.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 3- to 14-membered monocyclic, bicyclic or tricyclic aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N, S or P. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: azetidinyl, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydroisoquinolinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

In an embodiment, "heterocycle" (also referred to herein as "heterocyclyl"), is a monocyclic, bicyclic or tricyclic saturated or unsaturated ring of 5- to 14-ring atoms of carbon and from one to four heteroatoms selected from O, N, S or P. In this embodiment, examples of heterocyclic rings include, but are not limited to: pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, piperazinyl, dihydrofuranyl, tetrahydrofuranyl, dihydropyranyl, tetrahydrodropyranyl, dihydroquinolinyl, tetrahydroquinolinyl, dihydroisoquinolinyl, tetrahydroisoquinolinyl, dihydropyrazinyl, tetrahydropyrazinyl, dihydropyridyl, tetrahydropyridyl, pyrazolyl, pyridazinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl and the like.

An "alkylaryl group" (arylalkyl) is an alkyl group substituted with an aromatic group, preferably a phenyl group. A preferred alkylaryl group is a benzyl group. Suitable aromatic groups are described herein and suitable alkyl groups are described herein. Suitable substituents for an alkylaryl group are described herein.

An "alkyheterocyclyl" group" is an alkyl group substituted with a heterocyclyl group. Suitable heterocyclyl groups are described herein and suitable alkyl groups are described herein. Suitable substituents for an alkyheterocyclyl group are described herein.

An "alkycycloalkyl group" is an alkyl group substituted with a cycloalkyl group. Suitable cycloalkyl groups are described herein and suitable alkyl groups are described herein. Suitable substituents for an alkycycloalkyl group are described herein.

An "aryloxy group" is an aryl group that is attached to a compound via an oxygen (e.g., phenoxy).

An "alkoxy group" (alkyloxy), as used herein, is a straight chain or branched C_1-C_{12} or cyclic C_3-C_{12} alkyl group that is connected to a compound via an oxygen atom. Examples of alkoxy groups include but are not limited to methoxy, ethoxy and propoxy.

An "arylalkoxy group" (arylalkyloxy) is an arylalkyl group that is attached to a compound via an oxygen on the alkyl portion of the arylalkyl (e.g., phenylmethoxy).

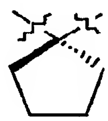
An "arylamino group" as used herein, is an aryl group that is attached to a compound via a nitrogen.

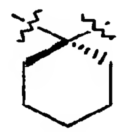
As used herein, an "arylalkylamino group" is an arylalkyl group that is attached to a compound via a nitrogen on the alkyl portion of the arylalkyl.

As used herein, many moieties or groups are referred to as being either "substituted or unsubstituted". When a moiety is referred to as substituted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted. The phrase "optionally substituted with one or more substituents" means, in one embodiment, one substituent, two substituents, three substituents, four substituents or five substituents. For example, the substitutable group can be a hydrogen atom that is replaced with a group other than hydrogen (i.e., a substituent group). Multiple substituent groups can be present. When multiple substituents are present, the substituents can be the same or different and substitution can be at any of the substitutable sites. Such means for substitution are well known in the art. For purposes of exemplification, which should not be construed as limiting the scope of this invention, some examples of groups that are substituents are: alkyl groups (which can also be substituted, with one or more substituents), alkoxy groups (which can be substituted), a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-alkylamino or N,N-dialkylamino (in which the alkyl groups can also be substituted), N-arylamino or N,N-diarylamino (in which the aryl groups can also be substituted), esters (-C(O)-OR, where R can be a group such as alkyl, aryl, etc., which can be substituted), ureas (-NHC(O)-NHR, where R can be a group such as alkyl, aryl, etc., which can be substituted), carbamates (-NHC(O)-OR, where R can be a group such as alkyl, aryl, etc., which can be substituted), sulfonamides (-NHS(O)2R, where R can be a group such as alkyl, aryl,

etc., which can be substituted), aryl (which can be substituted), cycloalkyl (which can be substituted) alkylaryl (which can be substituted), alkylheterocyclyl (which can be substituted), alkylcycloalkyl (which can be substituted), and aryloxy.

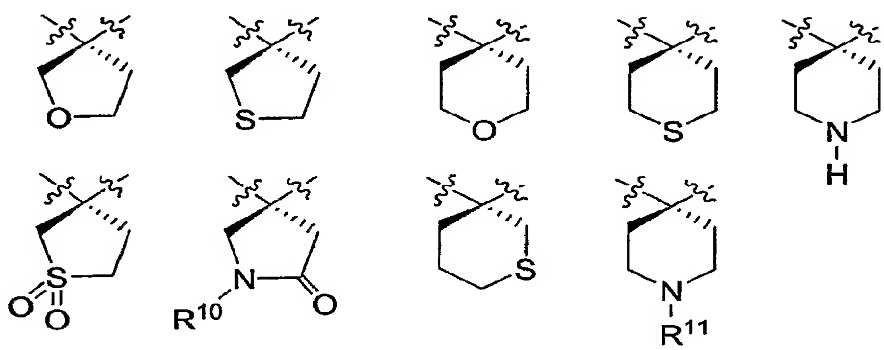
The moiety formed when, in the definition of R^1 and R^2 on the same carbon atom are combined to form -(CHR^9)$_u$- is illustrated by the following:





It is understood that such rings are not shown with R^9 substituent(s) to simplify the drawing, but may be substituted.

In addition, such cyclic moieties may optionally include a heteroatom(s). Examples of such heteroatom-containing cyclic moieties include, but are not limited to:



In an embodiment of the compounds of the Formula I, Ar^1 (which may be substituted with from 1 to 2 of R^6) is selected from: phenyl, benzothiophenyl, benzofuranyl, thiazolyl, benzothiazolyl, furanyl, pyridyl, pyrimidyl, quinolinyl, thiophenyl, benzodioxyl, benzooxadiazolyl, quinoxalinyl, benzotriazolyl, benzoimidazolyl and benzooxazolyl. In a further embodiment of the compounds of the Formula I, Ar^1 is selected from: phenyl and benzothiophenyl.

In an embodiment of the compounds of the Formula I, Ar^2 is selected from: phenyl, pyridyl, pyrrolyl and pyrazolyl. In a further embodiment of the compounds of the Formula I, Ar^2 is selected from: phenyl and pyrazolyl.

In an embodiment of the compounds of the Formula I, R^2 is selected from hydrogen, C_1-C_{10} alkyl and fluoro.

In an embodiment of the compounds of the Formula I, R^3 is NH_2.

In an embodiment of the compounds of the Formula I, p is 1 and R^4 is phenyl or thienyl, which is optionally substituted with from 1 to 3 of the substituent R^6.

In an embodiment of the compounds of the Formula I, R^5 is selected from amino, C_1-C_{10} alkylamino; C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH and C_1-C_{10} alkoxy.

In an embodiment of the compounds of the Formula II, Ar^1 (which may be substituted with from 1 to 2 of R^6) is selected from: phenyl, benzothiophenyl, benzofuranyl, thiazolyl, benzothiazolyl, furanyl, pyridyl, pyrimidyl, quinolinyl, thiophenyl, benzodioxyl, benzooxadiazolyl, quinoxalinyl, benzotriazolyl, benzoimidazolyl and benzooxazolyl. In a further embodiment of the compounds of the Formula II, Ar^1 is selected from: phenyl and benzothiophenyl.

In an embodiment of the compounds of the Formula II, X is CH, and R^{4b} and R^{4c} are H.

In an embodiment of the compounds of the Formula II, R^2 is selected from hydrogen, C_1-C_{10} alkyl and fluoro.

In an embodiment of the compounds of the Formula II, R^3 is NH_2.

In an embodiment of the compounds of the Formula II, R^4 is phenyl or thienyl, which is optionally substituted with from 1 to 3 of the substituent R^6.

In an embodiment of the compounds of the Formula II, R^5 is selected from amino, C_1-C_{10} alkylamino; C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH and C_1-C_{10} alkoxy.

In an embodiment of the compounds of the Formula III, Ar^1 (which may be substituted with from 1 to 2 of R^6) is selected from: phenyl, benzothiophenyl, benzofuranyl, thiazolyl, benzothiazolyl, furanyl, pyridyl, pyrimidyl, quinolinyl, thiophenyl, benzodioxyl, benzooxadiazolyl, quinoxalinyl, benzotriazolyl, benzoimidazolyl and benzooxazolyl. In a further embodiment of the compounds of the Formula III, Ar^1 is selected from: phenyl and benzothiophenyl.

In an embodiment of the compounds of the Formula III, X is CH.

In an embodiment of the compounds of the Formula III, R^2 is selected from hydrogen, C_1-C_{10} alkyl and fluoro.

In an embodiment of the compounds of the Formula III, R^5 is selected from amino, C_1-C_{10} alkylamino; C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH and C_1-C_{10} alkoxy.

In an embodiment of the compounds of the Formula IV, Ar^1 (which may be substituted with from 1 to 2 of R^6) is selected from: phenyl, benzothiophenyl, benzofuranyl, thiazolyl, benzothiazolyl, furanyl, pyridyl, pyrimidyl, quinolinyl, thiophenyl, benzodioxyl, benzooxadiazolyl, quinoxalinyl, benzotriazolyl, benzoimidazolyl and benzooxazolyl. In a further embodiment of the compounds of the Formula IV, Ar^1 is selected from: phenyl and benzothiophenyl.

In an embodiment of the compounds of the Formula IV, X is N and $R^{4'}$ is H.

In an embodiment of the compounds of the Formula IV, R^2 is selected from hydrogen, C_1-C_{10} alkyl and fluoro.

In an embodiment of the compounds of the Formula IV, R^3 is NH_2.

In an embodiment of the compounds of the Formula IV, R^4 is phenyl or thienyl, which is optionally substituted with from 1 to 3 of the substituent R^6.

In an embodiment of the compounds of the Formula IV, R^5 is selected from amino, C_1-C_{10} alkylamino; C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH and C_1-C_{10} alkoxy.

In an embodiment of the compounds of the Formula V, Ar^1 (which may be substituted with from 1 to 2 of R^6) is selected from: phenyl, benzothiophenyl, benzofuranyl, thiazolyl, benzothiazolyl, furanyl, pyridyl, pyrimidyl, quinolinyl, thiophenyl, benzodioxyl, benzooxadiazolyl, quinoxalinyl, benzotriazolyl, benzoimidazolyl and benzooxazolyl. In a further embodiment of the compounds of the Formula V, Ar^1 is selected from: phenyl and benzothiophenyl.

In an embodiment of the compounds of the Formula V, R^2 is selected from hydrogen, C_1-C_{10} alkyl and fluoro.

In an embodiment of the compounds of the Formula V, R^4 is phenyl, which is optionally substituted with from 1 to 3 of the substituent R^6.

In an embodiment of the compounds of the Formula V, R^5 is selected from amino, C_1-C_{10} alkylamino; C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH and C_1-C_{10} alkoxy.

Stereochemistry

Many organic compounds exist in optically active forms having the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these compounds, called stereoisomers, are identical except that they are non-superimposable mirror images of one another. A specific stereoisomer can also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture. Many of the compounds described herein can have one or more chiral centers and therefore can exist in different enantiomeric forms. If desired, a chiral carbon can be designated with an asterisk (*). When bonds to the chiral carbon are depicted as straight lines in the Formulas of the invention, it is understood that both the (R) and (S) configurations of the chiral carbon, and hence both enantiomers and mixtures thereof, are embraced within the Formula. As is used in the art, when it is desired to specify the absolute configuration about a chiral carbon, one of the bonds to the chiral carbon can be depicted as a wedge (bonds to atoms above the plane) and the other can be depicted as a series or wedge of short parallel lines is (bonds to atoms below the plane). The Cahn-Inglod-Prelog system can be used to assign the (R) or (S) configuration to a chiral carbon.

When the HDAC inhibitors of the present invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as the specific 50:50 mixture referred to as a racemic mixtures. The enantiomers can be resolved by methods known to those skilled in the art, such as formation of

diastereoisomeric salts which may be separated, for example, by crystallization (see, CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation by David Kozma (CRC Press, 2001)); formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

Designation of a specific absolute configuration at a chiral carbon of the compounds of the invention is understood to mean that the designated enantiomeric form of the compounds is in enantiomeric excess (ee) or in other words is substantially free from the other enantiomer. For example, the "R" forms of the compounds are substantially free from the "S" forms of the compounds and are, thus, in enantiomeric excess of the "S" forms. Conversely, "S" forms of the compounds are substantially free of "R" forms of the compounds and are, thus, in enantiomeric excess of the "R" forms. Enantiomeric excess, as used herein, is the presence of a particular enantiomer at greater than 50%. In a particular embodiment when a specific absolute configuration is designated, the enantiomeric excess of depicted compounds is at least about 90%.

When a compound of the present invention has two or more chiral carbons it can have more than two optical isomers and can exist in diastereoisomeric forms. For example, when there are two chiral carbons, the compound can have up to 4 optical isomers and 2 pairs of enantiomers ((S,S)/(R,R) and (R,S)/(S,R)). The pairs of enantiomers (e.g., (S,S)/(R,R)) are mirror image stereoisomers of one another. The stereoisomers that are not mirror-images (e.g., (S,S) and (R,S)) are diastereomers. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of such compounds and mixtures thereof.

As used herein, "a," an" and "the" include singular and plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well a two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

This invention is also intended to encompass pro-drugs of the fluoroalkylarylamide derivatives disclosed herein. A prodrug of any of the compounds can be made using well-known pharmacological techniques.

This invention, in addition to the above listed compounds, is intended to encompass the use of homologs and analogs of such compounds. In this context, homologs are molecules having

substantial structural similarities to the above-described compounds and analogs are molecules having substantial biological similarities regardless of structural similarities.

Pharmaceutically acceptable salts

The fluoroalkylarylamide derivatives described herein can, as noted above, be prepared in the form of their pharmaceutically acceptable salts. Pharmaceutically acceptable salts are salts that retain the desired biological activity of the parent compound and do not impart undesired toxicological effects. Examples of such salts are (a) acid addition salts organic and inorganic acids, for example, acid addition salts which may, for example, be hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid, trifluoroacetic acid, formic acid and the like. Pharmaceutically acceptable salts can also be prepared from by treatment with inorganic bases, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine, and the like. Pharmaceutically acceptable salts can also salts formed from elemental anions such as chlorine, bromine and iodine.

The active compounds disclosed can, as noted above, also be prepared in the form of their hydrates. The term “hydrate” includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate and the like.

The active compounds disclosed can, as noted above, also be prepared in the form of a solvate with any organic or inorganic solvent, for example alcohols such as methanol, ethanol, propanol and isopropanol, ketones such as acetone, aromatic solvents and the like.

The active compounds disclosed can also be prepared in any solid or liquid physical form. For example, the compound can be in a crystalline form, in amorphous form, and have any particle size. Furthermore, the compound particles may be micronized, or may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form.

The compounds of the present invention may also exhibit polymorphism. This invention further includes different polymorphs of the compounds of the present invention. The term “polymorph” refers to a particular crystalline state of a substance, having particular physical properties such as X-ray diffraction, IR spectra, melting point, and the like.

As used herein, "a," an" and "the" include singular and plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an active agent" or "a pharmacologically active agent" includes a single active agent as well a two or more different active agents in combination, reference to "a carrier" includes mixtures of two or more carriers as well as a single carrier, and the like.

METHODS OF TREATMENT

The invention also relates to methods of using the fluoroalkylarylamide derivatives described herein. As demonstrated herein, the fluoroalkylarylamide derivatives of the present invention are useful for the treatment of cancer. In addition, there is a wide range of other diseases for which

fluoroalkylarylamide derivatives may be found useful. Non-limiting examples are thioredoxin (TRX)-mediated diseases as described herein, and diseases of the central nervous system (CNS) as described herein.

1. Treatment of Cancer

As demonstrated herein, the fluoroalkylarylamide derivatives of the present invention are useful for the treatment of cancer. Accordingly, in one embodiment, the invention relates to a method of treating cancer in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of the fluoroalkylarylamide derivatives described herein.

The term "cancer" refers to any cancer caused by the proliferation of neoplastic cells, such as solid tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. In particular, cancers that may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma,

adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

In an embodiment, the instant compounds are useful in the treatment of cancers that include, but are not limited to: leukemias including acute leukemias and chronic leukemias such as acute lymphocytic leukemia (ALL), Acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML) and Hairy Cell Leukemia; lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotrophic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), Hodgkin's disease and non-Hodgkin's lymphomas, large-cell lymphomas, diffuse large B-cell lymphoma (DLBCL); Burkitt's lymphoma; mesothelioma, primary central nervous system (CNS) lymphoma; multiple myeloma; childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilm's tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (e.g., oral, laryngeal and esophageal), genito urinary cancers (e.g., prostate, bladder, renal, uterine, ovarian, testicular, rectal and colon), lung cancer, breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, liver cancer and thyroid cancer.

2. Treatment of thioredoxin (TRX)-mediated diseases

In another embodiment, the fluoroalkylarylamide derivatives are used in a method of treating a thioredoxin (TRX)-mediated disease or disorder in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of one or more of the fluoroalkylarylamide compounds described herein.

Examples of TRX-mediated diseases include, but are not limited to, acute and chronic inflammatory diseases, autoimmune diseases, allergic diseases, diseases associated with oxidative stress, and diseases characterized by cellular hyperproliferation.

Non-limiting examples are inflammatory conditions of a joint including rheumatoid arthritis (RA) and psoriatic arthritis; inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; spondyloarthropathies; scleroderma; psoriasis (including T-cell mediated psoriasis) and inflammatory dermatoses such an dermatitis, eczema, atopic dermatitis, allergic contact dermatitis, urticaria; vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis); eosinphilic myositis, eosinophilic fasciitis; cancers with leukocyte infiltration of the skin or organs, ischemic injury, including cerebral ischemia (e.g., brain injury as a result of trauma, epilepsy, hemorrhage or stroke, each of which may lead to neurodegeneration); HIV, heart failure, chronic, acute or malignant liver disease, autoimmune thyroiditis;

systemic lupus erythematosus, Sjorgren's syndrome, lung diseases (e.g., ARDS); acute pancreatitis; amyotrophic lateral sclerosis (ALS); Alzheimer's disease; cachexia/anorexia; asthma; atherosclerosis; chronic fatigue syndrome, fever; diabetes (e.g., insulin diabetes or juvenile onset diabetes); glomerulonephritis; graft versus host rejection (e.g., in transplantation); hemohorragic shock; hyperalgesia: inflammatory bowel disease; multiple sclerosis; myopathies (e.g., muscle protein metabolism, esp. in sepsis); osteoporosis; Parkinson's disease; pain; pre-term labor; psoriasis; reperfusion injury; cytokine-induced toxicity (e.g., septic shock, endotoxic shock); side effects from radiation therapy, temporal mandibular joint disease, tumor metastasis; or an inflammatory condition resulting from strain, sprain, cartilage damage, trauma such as burn, orthopedic surgery, infection or other disease processes. Allergic diseases and conditions, include but are not limited to respiratory allergic diseases such as asthma, allergic rhinitis, hypersensitivity lung diseases, hypersensitivity pneumonitis, eosinophilic pneumonias (e.g., Loeffler's syndrome, chronic eosinophilic pneumonia), delayed-type hypersensitivity, interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, systemic sclerosis, Sjogren's syndrome, polymyositis or dermatomyositis); systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies, and the like.

3. Treatment of diseases of the central nervous system (CNS)

In another embodiment, the fluoroalkylarylamide derivatives are used in a method of treating a disease of the central nervous system in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any one or more of the fluoroalkylarylamide compounds described herein.

In a particular embodiment, the CNS disease is a neurodegenerative disease. In a further embodiment, the neurodegenerative disease is an inherited neurodegenerative disease, such as those inherited neurodegenerative diseases that are polyglutamine expansion diseases. Generally, neurodegenerative diseases can be grouped as follows:

I. Disorders characterized by progressive dementia in the absence of other prominent neurologic signs, such as Alzheimer's disease; Senile dementia of the Alzheimer type; and Pick's disease (lobar atrophy).

II. Syndromes combining progressive dementia with other prominent neurologic abnormalities such as A) syndromes appearing mainly in adults (e.g., Huntington's disease, Multiple system atrophy combining dementia with ataxia and/or manifestations of Parkinson's disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentatonigral degeneration); and B) syndromes appearing mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive familial myoclonic epilepsy).

III. Syndromes of gradually developing abnormalities of posture and movement such as paralysis agitans (Parkinson's disease), striatonigral degeneration, progressive supranuclear palsy, torsion dystonia (torsion spasm; dystonia musculorum deformans), spasmodic torticollis and other dyskinesis, familial tremor, and Gilles de la Tourette syndrome.

IV. Syndromes of progressive ataxia such as cerebellar degenerations (e.g., cerebellar cortical degeneration and olivopontocerebellar atrophy (OPCA)); and spinocerebellar degeneration (Friedreich's atazia and related disorders).

V. Syndrome of central autonomic nervous system failure (Shy-Drager syndrome).

VI. Syndromes of muscular weakness and wasting without sensory changes (motorneuron disease such as amyotrophic lateral sclerosis, spinal muscular atrophy (e.g., infantile spinal muscular atrophy (Werdnig-Hoffman), juvenile spinal muscular atrophy (Wohlfart-Kugelberg-Welander) and other forms of familial spinal muscular atrophy), primary lateral sclerosis, and hereditary spastic paraplegia.

VII. Syndromes combining muscular weakness and wasting with sensory changes (progressive neural muscular atrophy; chronic familial polyneuropathies) such as peroneal muscular atrophy (Charcot-Marie-Tooth), hypertrophic interstitial polyneuropathy (Dejerine-Sottas), and miscellaneous forms of chronic progressive neuropathy.

VIII. Syndromes of progressive visual loss such as pigmentary degeneration of the retina (retinitis pigmentosa), and hereditary optic atrophy (Leber's disease).

<u>Definitions</u>:

The term "treating" in its various grammatical forms in relation to the present invention refers to preventing (i.e., chemoprevention), curing, reversing, attenuating, alleviating, minimizing, suppressing or halting the deleterious effects of a disease state, disease progression, disease causative agent (e.g., bacteria or viruses) or other abnormal condition. For example, treatment may involve alleviating a symptom (i.e., not necessary all symptoms) of a disease or attenuating the progression of a disease. Because some of the inventive methods involve the physical removal of the etiological agent, the artisan will recognize that they are equally effective in situations where the inventive compound is administered prior to, or simultaneous with, exposure to the etiological agent (prophylactic treatment) and situations where the inventive compounds are administered after (even well after) exposure to the etiological agent.

Treatment of cancer, as used herein, refers to partially or totally inhibiting, delaying or preventing the progression of cancer including cancer metastasis; inhibiting, delaying or preventing the recurrence of cancer including cancer metastasis; or preventing the onset or development of cancer (chemoprevention) in a mammal, for example a human.

As used herein, the term "therapeutically effective amount" is intended to encompass any amount that will achieve the desired therapeutic or biological effect. The therapeutic effect is dependent upon the disease or disorder being treated or the biological effect desired. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease or disorder and/or inhibition (partial or complete) of progression of the disease. The amount needed to elicit the therapeutic response can be determined based on the age, health, size and sex of the subject. Optimal amounts can also be determined based on monitoring of the subject's response to treatment.

In the present invention, when the compounds are used to treat or prevent cancer, the desired biological response is partial or total inhibition, delay or prevention of the progression of cancer including cancer metastasis; inhibition, delay or prevention of the recurrence of cancer including cancer metastasis; or the prevention of the onset or development of cancer (chemoprevention) in a mammal, for example a human.

Furthermore, in the present invention, when the compounds are used to treat and/or prevent thioredoxin (TRX)-mediated diseases and conditions, a therapeutically effective amount is an amount that regulates, for example, increases, decreases or maintains a physiologically suitable level of TRX in the subject in need of treatment to elicit the desired therapeutic effect. The therapeutic effect is dependent upon the specific TRX-mediated disease or condition being treated. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease or disorder and/or inhibition (partial or complete) of progression of the disease or disease.

Furthermore, in the present invention, when the compounds are used to treat and/or prevent diseases or disorders of the central nervous system (CNS), a therapeutically effective amount is dependent upon the specific disease or disorder being treated. As such, the therapeutic effect can be a decrease in the severity of symptoms associated with the disease or disorder and/or inhibition (partial or complete) of progression of the disease or disorder.

In addition, a therapeutically effective amount can be an amount that inhibits histone deacetylase.

Further, a therapeutically effective amount, can be an amount that selectively induces terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, or an amount that induces terminal differentiation of tumor cells.

The method of the present invention is intended for the treatment or chemoprevention of human patients with cancer. However, it is also likely that the method would be effective in the treatment of cancer in other subjects. "Subject", as used herein, refers to animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, pigs, dogs, cats, rabbits, guinea pigs, rats, mice or other bovine, ovine, equine, canine, feline, rodent or murine species.

HISTONE DEACETYLASES AND HISTONE DEACETYLASE INHIBITORS

As demonstrated herein, the fluoroalkylarylamide derivatives of the present invention show improved activity as histone deacetylase (HDAC) inhibitors. Accordingly, in one embodiment, the invention relates to a method of inhibiting the activity of histone deacetylase comprising contacting the

histone deacetylase with an effective amount of one or more of the fluoroalkylarylamide compounds described herein.

Histone deacetylases (HDACs), as that term is used herein, are enzymes that catalyze the removal of acetyl groups from lysine residues in the amino terminal tails of the nucleosomal core histones. As such, HDACs together with histone acetyl transferases (HATs) regulate the acetylation status of histones. Histone acetylation affects gene expression and inhibitors of HDACs, such as the hydroxamic acid-based hybrid polar compound suberoylanilide hydroxamic acid (SAHA) induce growth arrest, differentiation and/or apoptosis of transformed cells *in vitro* and inhibit tumor growth *in vivo*. HDACs can be divided into three classes based on structural homology. Class I HDACs (HDACs 1, 2, 3 and 8) bear similarity to the yeast RPD3 protein, are located in the nucleus and are found in complexes associated with transcriptional co-repressors. Class II HDACs (HDACs 4, 5, 6, 7 and 9) are similar to the yeast HDA1 protein, and have both nuclear and cytoplasmic subcellular localization. Both Class I and II HDACs are inhibited by hydroxamic acid-based HDAC inhibitors, such as SAHA. Class III HDACs form a structurally distant class of NAD dependent enzymes that are related to the yeast SIR2 proteins and are not inhibited by hydroxamic acid-based HDAC inhibitors.

Histone deacetylase inhibitors or HDAC inhibitors, as that term is used herein are compounds that are capable of inhibiting the deacetylation of histones *in vivo*, *in vitro* or both. As such, HDAC inhibitors inhibit the activity of at least one histone deacetylase. As a result of inhibiting the deacetylation of at least one histone, an increase in acetylated histone occurs and accumulation of acetylated histone is a suitable biological marker for assessing the activity of HDAC inhibitors. Therefore, procedures that can assay for the accumulation of acetylated histones can be used to determine the HDAC inhibitory activity of compounds of interest. It is understood that compounds that can inhibit histone deacetylase activity can also bind to other substrates and as such can inhibit other biologically active molecules such as enzymes. It is also to be understood that the compounds of the present invention are capable of inhibiting any of the histone deacetylases set forth above, or any other histone deacetylases.

For example, in patients receiving HDAC inhibitors, the accumulation of acetylated histones in peripheral mononuclear cells as well as in tissue treated with HDAC inhibitors can be determined against a suitable control.

HDAC inhibitory activity of a particular compound can be determined *in vitro* using, for example, an enzymatic assays which shows inhibition of at least one histone deacetylase. Further, determination of the accumulation of acetylated histones in cells treated with a particular composition can be determinative of the HDAC inhibitory activity of a compound.

Assays for the accumulation of acetylated histones are well known in the literature. See, for example, Marks, P.A. *et al.*, J. Natl. Cancer Inst., 92:1210-1215, 2000, Butler, L.M. *et al.*, Cancer Res. 60:5165-5170 (2000), Richon, V. M. *et al.*, Proc. Natl. Acad. Sci., USA, 95:3003-3007, 1998, and Yoshida, M. *et al.*, J. Biol. Chem., 265:17174-17179, 1990.

For example, an enzymatic assay to determine the activity of an HDAC inhibitor compound can

be conducted as follows. Briefly, the effect of an HDAC inhibitor compound on affinity purified human epitope-tagged (Flag) HDAC1 can be assayed by incubating the enzyme preparation in the absence of substrate on ice for about 20 minutes with the indicated amount of inhibitor compound. Substrate ([^{3}H]acetyl-labelled murine erythroleukemia cell-derived histone) can be added and the sample can be incubated for 20 minutes at 37°C in a total volume of 30 μL. The reaction can then be stopped and released acetate can be extracted and the amount of radioactivity release determined by scintillation counting. An alternative assay useful for determining the activity of an HDAC inhibitor compound is the "HDAC Fluorescent Activity Assay; Drug Discovery Kit-AK-500" available from BIOMOL Research Laboratories, Inc., Plymouth Meeting, PA.

In vivo studies can be conducted as follows. Animals, for example, mice, can be injected intraperitoneally with an HDAC inhibitor compound. Selected tissues, for example, brain, spleen, liver etc, can be isolated at predetermined times, post administration. Histones can be isolated from tissues essentially as described by Yoshida *et al.*, J. Biol. Chem. 265:17174-17179, 1990. Equal amounts of histones (about 1 μg) can be electrophoresed on 15% SDS-polyacrylamide gels and can be transferred to Hybond-P filters (available from Amersham). Filters can be blocked with 3% milk and can be probed with a rabbit purified polyclonal anti-acetylated histone H4 antibody (αAc-H4) and anti-acetylated histone H3 antibody (αAc-H3) (Upstate Biotechnology, Inc.). Levels of acetylated histone can be visualized using a horseradish peroxidase-conjugated goat anti-rabbit antibody (1:5000) and the SuperSignal chemiluminescent substrate (Pierce). As a loading control for the histone protein, parallel gels can be run and stained with Coomassie Blue (CB).

In addition, hydroxamic acid-based HDAC inhibitors have been shown to up regulate the expression of the p21^{WAF1} gene. The p21^{WAF1} protein is induced within 2 hours of culture with HDAC inhibitors in a variety of transformed cells using standard methods. The induction of the p21^{WAF1} gene is associated with accumulation of acetylated histones in the chromatin region of this gene. Induction of p21^{WAF1} can therefore be recognized as involved in the G1 cell cycle arrest caused by HDAC inhibitors in transformed cells.

COMBINATION THERAPY

The fluoroalkylarylamide compounds of the present invention can be administered alone or in combination with other therapies suitable for the disease or disorder being treated. Where separate dosage formulations are used, the fluoroalkylarylamide compound and the other therapeutic agent can be administered at essentially the same time (concurrently) or at separately staggered times (sequentially). The pharmaceutical combination is understood to include all these regimens. Administration in these various ways are suitable for the present invention as long as the beneficial therapeutic effect of the fluoroalkylarylamide compound and the other therapeutic agent are realized by the patient at substantially the same time. In an embodiment, such beneficial effect is achieved when the target blood level concentrations of each active drug are maintained at substantially the same time.

The instant compounds are also useful in combination with known therapeutic agents and anti-cancer agents. For example, instant compounds are useful in combination with known anti-cancer agents. Combinations of the presently disclosed compounds with other anti-cancer or chemotherapeutic agents are within the scope of the invention. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors and other angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling, apoptosis inducing agents, agents that interfere with cell cycle checkpoints, agents that interfere with receptor tyrosine kinases (RTKs) and cancer vaccines. The instant compounds are particularly useful when co-administered with radiation therapy.

In an embodiment, the instant compounds are also useful in combination with known anti-cancer agents including the following: estrogen receptor modulators, androgen receptor modulators, retinoid receptor modulators, cytotoxic agents, antiproliferative agents, prenyl-protein transferase inhibitors, HMG-CoA reductase inhibitors, HIV protease inhibitors, reverse transcriptase inhibitors, and other angiogenesis inhibitors.

"Estrogen receptor modulators" refers to compounds that interfere with or inhibit the binding of estrogen to the receptor, regardless of mechanism. Examples of estrogen receptor modulators include, but are not limited to, diethylstibestral, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fluoxymestero, lfulvestrant, 4-[7-(2,2-dimethyl-1-oxopropoxy-4-methyl-2-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2H-1-benzopyran-3-yl]-phenyl-2,2-dimethylpropanoate, 4,4'-dihydroxybenzophenone-2,4-dinitrophenyl-hydrazone, and SH646.

Other hormonal agents include: aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), luteinizing hormone release hormone (LHRH) analogues, ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone.

"Androgen receptor modulators" refers to compounds which interfere or inhibit the binding of androgens to the receptor, regardless of mechanism. Examples of androgen receptor modulators include finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate.

"Retinoid receptor modulators" refers to compounds which interfere or inhibit the binding of retinoids to the receptor, regardless of mechanism. Examples of such retinoid receptor modulators include bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard, thiotepa, busulfan, carmustine, lomustine, streptozocin, tasonermin, lonidamine, carboplatin, altretamine, dacarbazine, procarbazine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, doxorubicin, daunorubicin, idarubicin, anthracenedione, bleomycin, mitomycin C, dactinomycin, plicatomycin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin (see WO 00/50032).

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and bortezomib.

Examples of microtubule inhibitors/microtubule-stabilising agents include vincristine, vinblastine, vindesine, vinzolidine, vinorelbine, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), paclitaxel, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, 2,3,4,5,6-pentafluoro-N-(3-fluoro-4-methoxyphenyl) benzene sulfonamide, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, 9-methoxy-N,N-dimethyl-5-nitropyrazolo[3,4,5-kl]acridine-2-(6H) propanamine, 1-amino-9-ethyl-5-fluoro-2,3-dihydro-9-hydroxy-4-methyl-1H,12H-benzo[de]pyrano[3',4':b,7]-indolizino[1,2b]quinoline-10,13(9H,15H)dione, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-

(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, (5a, 5aB, 8aa,9b)-9-[2-[N-[2-(dimethylamino)ethyl]-N-methylamino]ethyl]-5-[4-hydro0xy-3,5-dimethoxyphenyl]-5,5a,6,8,8a,9-hexohydrofuro(3',4':6,7)naphtho(2,3-d)-1,3-dioxol-6-one, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 6,9-bis[(2-aminoethyl)amino]benzo[g]isoguinoline-5,10-dione, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c] quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins, and in particular the human mitotic kinesin KSP, are described in PCT Publications WO 01/30768, WO 01/98278, WO 03/050,064, WO 03/050,122, WO 03/049,527, WO 03/049,679, WO 03/049,678 and WO 03/39460 and pending PCT Appl. Nos. US03/06403 (filed March 4, 2003), US03/15861 (filed May 19, 2003), US03/15810 (filed May 19, 2003), US03/18482 (filed June 12, 2003) and US03/18694 (filed June 12, 2003). In an embodiment inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, SAHA, TSA, oxamflatin, PXD101, MG98, valproic acid and scriptaid. Further reference to other histone deacetylase inhibitors may be found in the following manuscript; Miller, T.A. et al. J. Med. Chem. 46(24):5097-5116 (2003).

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N-[5-(2,3-dihydro-benzofuryl)sulfonyl]-N'-(3,4-dichlorophenyl)urea, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, 4-[2-amino-4-oxo-4,6,7,8-tetrahydro-3H-pyrimidino[5,4-b][1,4]thiazin-6-yl-(S)-ethyl]-2,5-thienoyl-L-glutamic acid, aminopterin, 5-flurouracil, floxuridine, methotrexate, leucovarin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, gemcitabine, alanosine, 11-acetyl-8-(carbamoyloxymethyl)-4-formyl-6-methoxy-14-oxa-1,11-diazatetracyclo(7.4.1.0.0)-tetradeca-2,4,6-trien-9-yl acetic acid ester, swainsonine, lometrexol, dexrazoxane, methioninase, 2'-cyano-2'-deoxy-N4-palmitoyl-1-B-D-arabino furanosyl cytosine and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Examples of monoclonal antibody targeted therapeutic agents include those therapeutic agents which have cytotoxic agents or radioisotopes attached to a cancer cell specific or target cell specific monoclonal antibody. Examples include Bexxar.

"HMG-CoA reductase inhibitors" refers to inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase. Examples of HMG-CoA reductase inhibitors that may be used include but are not limited to lovastatin (MEVACOR®; see U.S. Pat. Nos. 4,231,938, 4,294,926 and 4,319,039), simvastatin (ZOCOR®; see U.S. Pat. Nos. 4,444,784, 4,820,850 and 4,916,239), pravastatin (PRAVACHOL®; see U.S. Pat. Nos. 4,346,227, 4,537,859, 4,410,629, 5,030,447 and 5,180,589), fluvastatin (LESCOL®; see U.S. Pat. Nos. 5,354,772, 4,911,165, 4,929,437, 5,189,164, 5,118,853, 5,290,946 and 5,356,896) and atorvastatin (LIPITOR®; see U.S. Pat. Nos. 5,273,995, 4,681,893, 5,489,691 and 5,342,952). The structural formulas of these and additional HMG-CoA reductase inhibitors that may be used in the instant methods are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs", *Chemistry & Industry*, pp. 85-89 (5 February 1996) and US Patent Nos. 4,782,084 and 4,885,314. The term HMG-CoA reductase inhibitor as used herein includes all pharmaceutically acceptable lactone and open-acid forms (i.e., where the lactone ring is opened to form the free acid) as well as salt and ester forms of compounds which have HMG-CoA reductase inhibitory activity, and therefor the use of such salts, esters, open-acid and lactone forms is included within the scope of this invention.

"Prenyl-protein transferase inhibitor" refers to a compound which inhibits any one or any combination of the prenyl-protein transferase enzymes, including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase).

Examples of prenyl-protein transferase inhibitors can be found in the following publications and patents: WO 96/30343, WO 97/18813, WO 97/21701, WO 97/23478, WO 97/38665, WO 98/28980, WO 98/29119, WO 95/32987, U.S. Pat. No. 5,420,245, U.S. Pat. No. 5,523,430, U.S. Pat. No. 5,532,359, U.S. Pat. No. 5,510,510, U.S. Pat. No. 5,589,485, U.S. Pat. No. 5,602,098, European Patent Publ. 0 618 221, European Patent Publ. 0 675 112, European Patent Publ. 0 604 181, European Patent Publ. 0 696 593, WO 94/19357, WO 95/08542, WO 95/11917, WO 95/12612, WO 95/12572, WO 95/10514, U.S. Pat. No. 5,661,152, WO 95/10515, WO 95/10516, WO 95/24612, WO 95/34535, WO 95/25086, WO 96/05529, WO 96/06138, WO 96/06193, WO 96/16443, WO 96/21701, WO 96/21456, WO 96/22278, WO 96/24611, WO 96/24612, WO 96/05168, WO 96/05169, WO 96/00736, U.S. Pat. No. 5,571,792, WO 96/17861, WO 96/33159, WO 96/34850, WO 96/34851, WO 96/30017, WO 96/30018, WO 96/30362, WO 96/30363, WO 96/31111, WO 96/31477, WO 96/31478, WO 96/31501, WO 97/00252, WO 97/03047, WO 97/03050, WO 97/04785, WO 97/02920, WO 97/17070, WO 97/23478, WO 97/26246, WO 97/30053, WO 97/44350, WO 98/02436, and U.S. Pat. No. 5,532,359. For an example of the role of a prenyl-protein transferase inhibitor on angiogenesis see *European J. of Cancer*, Vol. 35, No. 9, pp.1394-1401 (1999).

"Angiogenesis inhibitors" refers to compounds that inhibit the formation of new blood vessels, regardless of mechanism. Examples of angiogenesis inhibitors include, but are not limited to,

tyrosine kinase inhibitors, such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, erythropoietin (epoietin- α), granulocyte-CSF (filgrastin), granulocyte, macrophage-CSF (sargramostim), pentosan polysulfate, cyclooxygenase inhibitors, including nonsteroidal anti-inflammatories (NSAIDs) like aspirin and ibuprofen as well as selective cyclooxy-genase-2 inhibitors like celecoxib and rofecoxib (*PNAS*, Vol. 89, p. 7384 (1992); *JNCI*, Vol. 69, p. 475 (1982); *Arch. Opthalmol.*, Vol. 108, p.573 (1990); *Anat. Rec.*, Vol. 238, p. 68 (1994); *FEBS Letters*, Vol. 372, p. 83 (1995); *Clin, Orthop*. Vol. 313, p. 76 (1995); *J. Mol. Endocrinol.*, Vol. 16, p.107 (1996); *Jpn. J. Pharmacol.*, Vol. 75, p. 105 (1997); *Cancer Res.*, Vol. 57, p. 1625 (1997); *Cell*, Vol. 93, p. 705 (1998); *Intl. J. Mol. Med.*, Vol. 2, p. 715 (1998); *J. Biol. Chem.*, Vol. 274, p. 9116 (1999)), steroidal anti-inflammatories (such as corticosteroids, mineralocorticoids, dexamethasone, prednisone, prednisolone, methylpred, betamethasone), carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists (see Fernandez et al., *J. Lab. Clin. Med.* 105:141-145 (1985)), and antibodies to VEGF (see, *Nature Biotechnology*, Vol. 17, pp.963-968 (October 1999); Kim et al., *Nature*, *362*, 841-844 (1993); WO 00/44777; and WO 00/61186).

Other therapeutic agents that modulate or inhibit angiogenesis and may also be used in combination with the compounds of the instant invention include agents that modulate or inhibit the coagulation and fibrinolysis systems (see review in *Clin. Chem. La. Med.* 38:679-692 (2000)). Examples of such agents that modulate or inhibit the coagulation and fibrinolysis pathways include, but are not limited to, heparin (see *Thromb. Haemost.* 80:10-23 (1998)), low molecular weight heparins and carboxypeptidase U inhibitors (also known as inhibitors of active thrombin activatable fibrinolysis inhibitor [TAFIa]) (see *Thrombosis Res.* 101:329-354 (2001)). TAFIa inhibitors have been described in PCT Publication WO 03/013,526 and U.S. Ser. No. 60/349,925 (filed January 18, 2002).

"Agents that interfere with cell cycle checkpoints" refer to compounds that inhibit protein kinases that transduce cell cycle checkpoint signals, thereby sensitizing the cancer cell to DNA damaging agents. Such agents include inhibitors of ATR, ATM, the Chk1 and Chk2 kinases and cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032.

"Agents that interfere with receptor tyrosine kinases (RTKs)" refer to compounds that inhibit RTKs and therefore mechanisms involved in oncogenesis and tumor progression. Such agents include inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met. Further agents include inhibitors of RTKs shown as described by Bume-Jensen and Hunter, Nature, 411:355-365, 2001.

"Inhibitors of cell proliferation and survival signaling pathway" refer to pharmaceutical agents that inhibit cell surface receptors and signal transduction cascades downstream of those surface receptors. Such agents include inhibitors of inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGFR, inhibitors of CD20 (rituximab), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K (for example LY294002),

serine/threonine kinases (including but not limited to inhibitors of Akt such as described in (WO 03/086404, WO 03/086403, WO 03/086394, WO 03/086279, WO 02/083675, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573). Such agents include small molecule inhibitor compounds and antibody antagonists.

"Apoptosis inducing agents" include activators of TNF receptor family members (including the TRAIL receptors).

The invention also encompasses combinations with NSAID's which are selective COX-2 inhibitors. For purposes of this specification NSAID's which are selective inhibitors of COX-2 are defined as those which possess a specificity for inhibiting COX-2 over COX-1 of at least 100 fold as measured by the ratio of IC_{50} for COX-2 over IC_{50} for COX-1 evaluated by cell or microsomal assays. Such compounds include, but are not limited to those disclosed in U.S. Pat. 5,474,995, U.S. Pat. 5,861,419, U.S. Pat. 6,001,843, U.S. Pat. 6,020,343, U.S. Pat. 5,409,944, U.S. Pat. 5,436,265, U.S. Pat. 5,536,752, U.S. Pat. 5,550,142, U.S. Pat. 5,604,260, U.S. 5,698,584, U.S. Pat. 5,710,140, WO 94/15932, U.S. Pat. 5,344,991, U.S. Pat. 5,134,142, U.S. Pat. 5,380,738, U.S. Pat. 5,393,790, U.S. Pat. 5,466,823, U.S. Pat. 5,633,272, and U.S. Pat. 5,932,598, all of which are hereby incorporated by reference.

Inhibitors of COX-2 that are particularly useful in the instant method of treatment are: 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(*5H*)-furanone; and 5-chloro-3-(4-methylsulfonyl)phenyl-2-(2-methyl-5-pyridinyl)pyridine; or a pharmaceutically acceptable salt thereof.

Compounds that have been described as specific inhibitors of COX-2 and are therefore useful in the present invention include, but are not limited to: parecoxib, CELEBREX® and BEXTRA® or a pharmaceutically acceptable salt thereof.

Other examples of angiogenesis inhibitors include, but are not limited to, endostatin, ukrain, ranpirnase, IM862, 5-methoxy-4-[2-methyl-3-(3-methyl-2-butenyl)oxiranyl]-1-oxaspiro[2,5]oct-6-yl(chloroacetyl)carbamate, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, 7,7-(carbonyl-bis[imino-N-methyl-4,2-pyrrolocarbonylimino[N-methyl-4,2-pyrrole]-carbonylimino]-bis-(1,3-naphthalene disulfonate), and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416).

As used above, "integrin blockers" refers to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha_v\beta_3$ integrin, to compounds which selectively antagonize, inhibit or counteract binding of a physiological ligand to the $\alpha v\beta 5$ integrin, to compounds which antagonize, inhibit or counteract binding of a physiological ligand to both the $\alpha_v\beta_3$ integrin and the $\alpha_v\beta_5$ integrin, and to compounds which antagonize, inhibit or counteract the activity of the particular integrin(s) expressed on capillary endothelial cells. The term also refers to antagonists of the $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins. The term also refers to antagonists of any combination of $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, $\alpha_v\beta_8$, $\alpha_1\beta_1$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$ and $\alpha_6\beta_4$ integrins.

Some specific examples of tyrosine kinase inhibitors include N-(trifluoromethylphenyl)-5-methylisoxazol-4-carboxamide, 3-[(2,4-dimethylpyrrol-5-yl)methylidenyl)indolin-2-one, 17-(allylamino)-17-demethoxygeldanamycin, 4-(3-chloro-4-fluorophenylamino)-7-methoxy-6-[3-(4-morpholinyl)propoxyl]quinazoline, N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, BIBX1382, 2,3,9,10,11,12-hexahydro-10-(hydroxymethyl)-10-hydroxy-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one, SH268, genistein, imatinib (STI571), CEP2563, 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidinemethane sulfonate, 4-(3-bromo-4-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, 4-(4'-hydroxyphenyl)amino-6,7-dimethoxyquinazoline, SU6668, STI571A, N-4-chlorophenyl-4-(4-pyridylmethyl)-1-phthalazinamine, and EMD121974.

Combinations with compounds other than anti-cancer compounds are also encompassed in the instant methods. For example, combinations of the instantly claimed compounds with PPAR-γ (i.e., PPAR-gamma) agonists and PPAR-δ (i.e., PPAR-delta) agonists are useful in the treatment of certain malingnancies. PPAR-γ and PPAR-δ are the nuclear peroxisome proliferator-activated receptors γ and δ. The expression of PPAR-γ on endothelial cells and its involvement in angiogenesis has been reported in the literature (see *J. Cardiovasc. Pharmacol.* 1998; 31:909-913; *J. Biol. Chem.* 1999;274:9116-9121; *Invest. Ophthalmol Vis. Sci.* 2000; 41:2309-2317). More recently, PPAR-γ agonists have been shown to inhibit the angiogenic response to VEGF in vitro; both troglitazone and rosiglitazone maleate inhibit the development of retinal neovascularization in mice. (*Arch. Ophthamol.* 2001; 119:709-717). Examples of PPAR-γ agonists and PPAR- γ/α agonists include, but are not limited to, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and 2(R)-7-(3-(2-chloro-4-(4-fluorophenoxy) phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697).

Another embodiment of the instant invention is the use of the presently disclosed compounds in combination with gene therapy for the treatment of cancer. For an overview of genetic strategies to treating cancer see Hall et al (*Am J Hum Genet* 61:785-789, 1997) and Kufe et al (*Cancer Medicine*, 5th Ed, pp 876-889, BC Decker, Hamilton 2000). Gene therapy can be used to deliver any tumor suppressing gene. Examples of such genes include, but are not limited to, p53, which can be delivered via recombinant virus-mediated gene transfer (see U.S. Pat. No. 6,069,134, for example), Duc-4, NF-1, NF-2, RB, WT1, BRCA1, BRCA2, a uPA/uPAR antagonist ("Adenovirus-Mediated Delivery of a uPA/uPAR Antagonist Suppresses Angiogenesis-Dependent Tumor Growth and Dissemination in Mice," *Gene Therapy*, August 1998;5(8):1105-13), and interferon gamma (*J. Immunol.* 000; 164:217-222).

The compounds of the instant invention may also be administered in combination with an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of

expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

A compound of the present invention may be employed in conjunction with anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of a compound of the present invention, alone or with radiation therapy. For the prevention or treatment of emesis, a compound of the present invention may be used in conjunction with other anti-emetic agents, especially neurokinin-1 receptor antagonists, 5HT3 receptor antagonists, such as ondansetron, granisetron, tropisetron, and zatisetron, GABAB receptor agonists, such as baclofen, a corticosteroid such as Decadron (dexamethasone), Kenalog, Aristocort, Nasalide, Preferid, Benecorten or others such as disclosed in U.S.Patent Nos. 2,789,118, 2,990,401, 3,048,581, 3,126,375, 3,929,768, 3,996,359, 3,928,326 and 3,749,712, an antidopaminergic, such as the phenothiazines (for example prochlorperazine, fluphenazine, thioridazine and mesoridazine), metoclopramide or dronabinol. In an embodiment, an anti-emesis agent selected from a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid is administered as an adjuvant for the treatment or prevention of emesis that may result upon administration of the instant compounds.

Neurokinin-1 receptor antagonists of use in conjunction with the compounds of the present invention are fully described, for example, in U.S. Pat. Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, 5,637,699, 5,719,147; European Patent Publication Nos. EP 0 360 390, 0 394 989, 0 428 434, 0 429 366, 0 430 771, 0 436 334, 0 443 132, 0 482 539, 0 498 069, 0 499 313, 0 512 901, 0 512 902, 0 514 273, 0 514 274, 0 514 275, 0 514 276, 0 515 681, 0 517 589, 0 520 555, 0 522 808, 0 528 495, 0 532 456, 0 533 280, 0 536 817, 0 545 478, 0 558 156, 0 577 394, 0 585 913,0 590 152, 0 599 538, 0 610 793, 0 634 402, 0 686 629, 0 693 489, 0 694 535, 0 699 655, 0 699 674, 0 707 006, 0 708 101, 0 709 375, 0 709 376, 0 714 891, 0 723 959, 0 733 632 and 0 776 893; PCT International Patent Publication Nos. WO 90/05525, 90/05729, 91/09844, 91/18899, 92/01688, 92/06079, 92/12151, 92/15585, 92/17449, 92/20661, 92/20676, 92/21677, 92/22569, 93/00330, 93/00331, 93/01159, 93/01165, 93/01169, 93/01170, 93/06099, 93/09116, 93/10073, 93/14084, 93/14113, 93/18023, 93/19064, 93/21155, 93/21181, 93/23380, 93/24465, 94/00440, 94/01402, 94/02461, 94/02595, 94/03429, 94/03445, 94/04494, 94/04496, 94/05625, 94/07843, 94/08997, 94/10165, 94/10167, 94/10168, 94/10170, 94/11368, 94/13639, 94/13663, 94/14767, 94/15903, 94/19320, 94/19323, 94/20500, 94/26735, 94/26740, 94/29309, 95/02595, 95/04040, 95/04042, 95/06645, 95/07886, 95/07908, 95/08549, 95/11880, 95/14017, 95/15311, 95/16679, 95/17382, 95/18124, 95/18129, 95/19344, 95/20575, 95/21819, 95/22525, 95/23798, 95/26338, 95/28418, 95/30674, 95/30687, 95/33744, 96/05181, 96/05193, 96/05203, 96/06094, 96/07649, 96/10562, 96/16939, 96/18643, 96/20197, 96/21661, 96/29304, 96/29317, 96/29326, 96/29328, 96/31214, 96/32385, 96/37489, 97/01553, 97/01554, 97/03066, 97/08144, 97/14671, 97/17362, 97/18206, 97/19084, 97/19942 and 97/21702; and in British Patent Publication Nos. 2 266 529, 2 268 931, 2 269 170, 2 269 590, 2 271 774, 2 292 144, 2 293 168, 2 293 169, and 2 302 689. The preparation of such compounds is fully described in the aforementioned patents and publications, which are incorporated herein by reference.

In an embodiment, the neurokinin-1 receptor antagonist for use in conjunction with the compounds of the present invention is selected from: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methyl)morpholine, or a pharmaceutically acceptable salt thereof, which is described in U.S. Pat. No. 5,719,147.

A compound of the instant invention may also be administered with an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin alfa).

A compound of the instant invention may also be administered with an agent useful in the treatment of neutropenia. Such a neutropenia treatment agent is, for example, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

A compound of the instant invention may also be administered with an immunologic-enhancing drug, such as levamisole, bacillus Calmette-Guerin, octreotide, isoprinosine and Zadaxin.

A compound of the instant invention may also be useful for treating or preventing cancer, including bone cancer, in combination with bisphosphonates (understood to include bisphosphonates, diphosphonates, bisphosphonic acids and diphosphonic acids). Examples of bisphosphonates include but are not limited to: etidronate (Didronel), pamidronate (Aredia), alendronate (Fosamax), risedronate (Actonel), zoledronate (Zometa), ibandronate (Boniva), incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate including any and all pharmaceutically acceptable salts, derivatives, hydrates and mixtures thereof.

A compound of the instant invention may also be useful for treating or preventing breast cancer in combination with aromatase inhibitors. Examples of aromatase inhibitors include but are not limited to: anastrozole, letrozole and exemestane.

A compound of the instant invention may also be useful for treating or preventing cancer in combination with siRNA therapeutics.

A compound of the instant invention may also be useful for treating or preventing cancer in combination withcompounds which induce terminal differentiation of the neoplastic cells. Suitable differentiation agents include the compounds disclosed in any one or more of the following references, the contents of which are incorporated by reference herein.

a) Polar compounds (Marks et al (1987); Friend, C., Scher, W., Holland, J. W., and Sato, T. (1971) *Proc. Natl. Acad. Sci.* (USA) 68: 378-382; Tanaka, M., Levy, J., Terada, M., Breslow, R., Rifkind, R. A., and Marks, P. A. (1975) *Proc. Natl. Acad. Sci.* (USA) 72: 1003-1006; Reuben, R. C., Wife, R. L., Breslow, R., Rifkind, R. A., and Marks, P. A. (1976) *Proc. Natl. Acad. Sci.* (USA) 73: 862-866);

b) Derivatives of vitamin D and retinoic acid (Abe, E., Miyaura, C., Sakagami, H., Takeda, M., Konno, K., Yamazaki, T., Yoshika, S., and Suda, T. (1981) *Proc. Natl. Acad. Sci. (*USA) 78: 4990-4994; Schwartz, E. L., Snoddy, J. R., Kreutter, D., Rasmussen, H., and Sartorelli, A. C. (1983)

Proc. Am. Assoc. Cancer Res. 24: 18; Tanenaga, K., Hozumi, M., and Sakagami, Y. (1980) *Cancer Res.* 40: 914-919);

c) Steroid hormones (Lotem, J. and Sachs, L. (1975) *Int. J. Cancer 15:* 731-740);

d) Growth factors (Sachs, L. (1978) *Nature (Lond.)* 274: 535, Metcalf, D. (1985) *Science,* 229: 16-22);

e) Proteases (Scher, W., Scher, B. M., and Waxman, S. (1983) *Exp. Hematol.* 11: 490-498; Scher, W., Scher, B. M., and Waxman, S. (1982) *Biochem. & Biophys. Res. Comm.* 109: 348-354);

f) Tumor promoters (Huberman, E. and Callaham, M. F. (1979) *Proc. Natl. Acad. Sci.* (USA) 76: 1293-1297; Lottem, J. and Sachs, L. (1979) *Proc. Natl. Acad. Sci.* (USA) 76: 5158-5162); and

g) inhibitors of DNA or RNA synthesis (Schwartz, E. L. and Sartorelli, A. C. (1982) *Cancer Res. 42:* 2651-2655, Terada, M., Epner, E., Nudel, U., Salmon, J., Fibach, E., Rifkind, R. A., and Marks, P. A. (1978) *Proc. Natl. Acad. Sci.* (USA) 75: 2795-2799; Morin, M. J. and Sartorelli, A. C. (1984) *Cancer Res. 44*: 2807-2812; Schwartz, E. L., Brown, B. J., Nierenberg, M., Marsh, J. C., and Sartorelli, A. C. (1983) *Cancer Res.* 43: 2725-2730; Sugano, H., Furusawa, M., Kawaguchi, T., and Ikawa, Y. (1973) *Bibl. Hematol.* 39: 943-954; Ebert, P. S., Wars, I., and Buell, D. N. (1976) *Cancer Res.* 36: 1809-1813; Hayashi, M., Okabe, J., and Hozumi, M. (1979) Gann 70: 235-238).

A compound of the instant invention may also be useful for treating or preventing cancer in combination with γ-secretase inhibitors.

Also included in the scope of the claims is a method of treating cancer that comprises administering a therapeutically effective amount of a compound of Formula I in combination with radiation therapy and/or in combination with a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxiccytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, PPAR-γ agonists, PPAR-δ agonists, an inhibitor of inherent multidrug resistance, an anti-emetic agent, an agent useful in the treatment of anemia, an agent useful in the treatment of neutropenia, an immunologic-enhancing drug, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and an agent that interferes with a cell cycle checkpoint.

The use of all of these approaches in combination with the fluoroalkylarylamide compounds described herein are within the scope of the present invention.

DOSAGES AND DOSING SCHEDULES

The dosage regimen utilizing the fluoroalkylarylamide derivatives of the present invention can be selected in accordance with a variety of factors including type, species, age, weight, sex and the type of cancer being treated; the severity (i.e., stage) of the disease to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the

effective amount of the drug required to treat, for example, to prevent, inhibit (fully or partially) or arrest the progress of the disease.

For oral administration, suitable daily dosages are for example between about 5-4000 mg/m^2 administered orally once-daily, twice-daily or three times-daily, continuous (every day) or intermittently (e.g., 3-5 days a week). For example, when used to treat the desired disease, the dose of the fluoroalkylarylamide compound can range between about 2 mg to about 2000 mg per day.

The fluoroalkylarylamide derivative is administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), and three times daily (TID). For administration once a day, a suitably prepared medicament would therefore contain all of the needed daily dose. For administration twice a day, a suitably prepared medicament would therefore contain half of the needed daily dose. For administration three times a day, a suitably prepared medicament would therefore contain one third of the needed daily dose.

In addition, the administration can be continuous, i.e., every day, or intermittently. The terms “intermittent” or “intermittently” as used herein means stopping and starting at either regular or irregular intervals. For example, intermittent administration of an HDAC inhibitor may be administration one to six days per week or it may mean administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week) or it may mean administration on alternate days.

Typically, an intravenous formulation may be prepared which contains a concentration of the fluoroalkylarylamide derivative of between about 1.0 mg/mL to about 10 mg/mL. In one example, a sufficient volume of intravenous formulation can be administered to a patient in a day such that the total dose for the day is between about 10 and about 1500 mg/m^2.

Subcutaneous formulations, preferably prepared according to procedures well known in the art at a pH in the range between about 5 and about 12, also include suitable buffers and isotonicity agents, as described below. T hey can be formulated to deliver a daily dose of HDAC inhibitor in one or more daily subcutaneous administrations, e.g., one, two or three times each day.

The compounds can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, or course, be continuous rather than intermittent throughout the dosage regime.

It should be apparent to a person skilled in the art that the various modes of administration, dosages and dosing schedules described herein merely set forth specific embodiments and should not be construed as limiting the broad scope of the invention. Any permutations, variations and combinations of the dosages and dosing schedules are included within the scope of the present invention.

The term "administration" and variants thereof (e.g., "administering" a compound) in reference to a compound of the invention means introducing the compound or a prodrug of the compound into the system of the animal in need of treatment. When a compound of the invention or prodrug thereof

is provided in combination with one or more other active agents (e.g., a cytotoxic agent, etc.), "administration" and its variants are each understood to include concurrent and sequential introduction of the compound or prodrug thereof and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

PHARMACEUTICAL COMPOSITIONS

The compounds of the invention, and derivatives, fragments, analogs, homologs pharmaceutically acceptable salts or hydrate thereof, can be incorporated into pharmaceutical compositions suitable for oral administration, together with a pharmaceutically acceptable carrier or excipient. Such compositions typically comprise a therapeutically effective amount of any of the compounds above, and a pharmaceutically acceptable carrier. In one embodiment, the effective amount is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.

Any inert excipient that is commonly used as a carrier or diluent may be used in the formulations of the present invention, such as for example, a gum, a starch, a sugar, a cellulosic material, an acrylate, or mixtures thereof. A preferred diluent is microcrystalline cellulose. The compositions may further comprise a disintegrating agent (e.g., croscarmellose sodium) and a lubricant (e.g., magnesium stearate), and in addition may comprise one or more additives selected from a binder, a buffer, a protease inhibitor, a surfactant, a solubilizing agent, a plasticizer, an emulsifier, a stabilizing agent, a viscosity increasing agent, a sweetener, a film forming agent, or any combination thereof. Furthermore, the compositions of the present invention may be in the form of controlled release or immediate release formulations.

In one embodiment, the pharmaceutical compositions are administered orally, and are thus formulated in a form suitable for oral administration, i.e., as a solid or a liquid preparation. Suitable solid oral formulations include tablets, capsules, pills, granules, pellets and the like. Suitable liquid oral formulations include solutions, suspensions, dispersions, emulsions, oils and the like. In one embodiment of the present invention, the composition is formulated in a capsule. In accordance with this embodiment, the compositions of the present invention comprise in addition to the fluoroalkylarylamide derivative active compound and the inert carrier or diluent, a hard gelatin capsule.

As used herein, "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying

agents, and the like, compatible with pharmaceutical administration, such as sterile pyrogen-free water. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, finger's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

Solid carriers/diluents include, but are not limited to, a gum, a starch (e.g., corn starch, pregelatinized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g., microcrystalline cellulose), an acrylate (e.g., polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

For liquid formulations, pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Examples of oils are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, mineral oil, olive oil, sunflower oil, and fish-liver oil. Solutions or suspensions can also include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide.

In addition, the compositions may further comprise binders (e.g., acacia, cornstarch, gelatin, carbomer, ethyl cellulose, guar gum, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, povidone), disintegrating agents (e.g., cornstarch, potato starch, alginic acid, silicon dioxide, croscarmellose sodium, crospovidone, guar gum, sodium starch glycolate, Primogel), buffers (e.g., tris-HCI, acetate, phosphate) of various pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts), protease inhibitors, surfactants (e.g., sodium lauryl sulfate), permeation enhancers, solubilizing agents (e.g., glycerol, polyethylene glycerol), a glidant (e.g., colloidal silicon dioxide), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite, butylated hydroxyanisole), stabilizers (e.g., hydroxypropyl cellulose, hyroxypropylmethyl cellulose), viscosity increasing agents (e.g., carbomer, colloidal silicon dioxide, ethyl cellulose, guar gum), sweeteners (e.g., sucrose, aspartame, citric acid), flavoring agents (e.g., peppermint, methyl salicylate, or orange flavoring), preservatives (e.g., Thimerosal, benzyl alcohol, parabens), lubricants (e.g., stearic acid, magnesium stearate, polyethylene glycol, sodium lauryl sulfate),

flow-aids (e.g., colloidal silicon dioxide), plasticizers (e.g., diethyl phthalate, triethyl citrate), emulsifiers (e.g., carbomer, hydroxypropyl cellulose, sodium lauryl sulfate), polymer coatings (e.g., poloxamers or poloxamines), coating and film forming agents (e.g., ethyl cellulose, acrylates, polymethacrylates) and/or adjuvants.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

The compounds of the present invention may be administered intravenously on the first day of treatment, with oral administration on the second day and all consecutive days thereafter.

The compounds of the present invention may be administered for the purpose of preventing disease progression or stabilizing tumor growth.

The preparation of pharmaceutical compositions that contain an active component is well understood in the art, for example, by mixing, granulating, or tablet-forming processes. The active therapeutic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. For oral administration, the active agents are mixed with additives customary for this purpose, such as vehicles, stabilizers, or inert diluents, and converted by customary methods into suitable forms for administration, such as tablets, coated tablets, hard or soft gelatin capsules, aqueous, alcoholic or oily solutions and the like as detailed above.

The amount of the compound administered to the patient is less than an amount that would cause toxicity in the patient. In the certain embodiments, the amount of the compound that is administered to the patient is less than the amount that causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. Preferably, the concentration of the

compound in the patient's plasma is maintained at about 10 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 25 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 50 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 100 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 500 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 1000 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 2500 nM. In another embodiment, the concentration of the compound in the patient's plasma is maintained at about 5000 nM. The optimal amount of the compound that should be administered to the patient in the practice of the present invention will depend on the particular compound used and the type of cancer being treated.

The instant invention also includes a pharmaceutical composition useful for treating or preventing cancer that comprises a therapeutically effective amount of a compound of Formula I and a second compound selected from: an estrogen receptor modulator, an androgen receptor modulator, a retinoid receptor modulator, a cytotoxic/cytostatic agent, an antiproliferative agent, a prenyl-protein transferase inhibitor, an HMG-CoA reductase inhibitor, an HIV protease inhibitor, a reverse transcriptase inhibitor, an angiogenesis inhibitor, a PPAR-γ agonist, a PPAR-δ agonist, an inhibitor of cell proliferation and survival signaling, a bisphosphonate, an aromatase inhibitor, an siRNA therapeutic, γ-secretase inhibitors, agents that interfere with receptor tyrosine kinases (RTKs) and an agent that interferes with a cell cycle checkpoint.

In Vitro METHODS:

The present invention also provides methods of using the fluoroalkylarylamide derivatives of the present invention for inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells thereby inhibiting the proliferation of such cells. The methods can be practiced *in vivo* or *in vitro*.

In one embodiment, the present invention provides *in vitro* methods for selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, thereby inhibiting proliferation of such cells, by contacting the cells with an effective amount of any one or more of the fluoroalkylarylamide derivatives described herein.

In a particular embodiment, the present invention relates to an *in vitro* method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells. The method comprises contacting the cells under suitable conditions with an effective amount of one or more of the fluoroalkylarylamide compounds described herein.

In another embodiment, the invention relates to an *in vitro* method of selectively inducing cell growth arrest of neoplastic cells and thereby inhibiting proliferation of such cells. The method comprises contacting the cells under suitable conditions with an effective amount of one or more of the fluoroalkylarylamide compounds described herein.

In another embodiment, the invention relates to an *in vitro* method of selectively inducing apoptosis of neoplastic cells and thereby inhibiting proliferation of such cells. The method comprises contacting the cells under suitable conditions with an effective amount of one or more of the fluoroalkylarylamide compounds described herein.

In another embodiment, the invention relates to an *in vitro* method of inducing terminal differentiation of tumor cells in a tumor comprising contacting the cells with an effective amount of any one or more of the fluoroalkylarylamide compounds described herein.

Although the methods of the present invention can be practiced *in vitro*, it is contemplated that the preferred embodiment for the methods of selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells, and of inhibiting HDAC will comprise contacting the cells *in vivo*, i.e., by administering the compounds to a subject harboring neoplastic cells or tumor cells in need of treatment.

Thus, the present invention provides *in vivo* methods for selectively inducing terminal differentiation, cell growth arrest and/or apoptosis of neoplastic cells in a subject, thereby inhibiting proliferation of such cells in the subject, by administering to the subject an effective amount of any one or more of the fluoroalkylarylamide derivatives described herein.

In a particular embodiment, the present invention relates to a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells in a subject. The method comprises administering to the subject an effective amount of one or more of the fluoroalkylarylamide derivatives described herein.

In another embodiment, the invention relates to a method of selectively inducing cell growth arrest of neoplastic cells and thereby inhibiting proliferation of such cells in a subject. The method comprises administering to the subject an effective amount of one or more of the fluoroalkylarylamide derivatives described herein.

In another embodiment, the invention relates to a method of selectively inducing apoptosis of neoplastic cells and thereby inhibiting proliferation of such cells in a subject. The method comprises administering to the subject an effective amount of one or more of the fluoroalkylarylamide derivatives described herein.

In another embodiment, the invention relates to a method of treating a patient having a tumor characterized by proliferation of neoplastic cells. The method comprises administering to the patient one or more of the fluoroalkylarylamide derivatives described herein. The amount of compound is effective to selectively induce terminal differentiation, induce cell growth arrest and/or induce apoptosis of such neoplastic cells and thereby inhibit their proliferation.

The invention is illustrated in the examples in the Experimental Details Section that follows. This section is set forth to aid in an understanding of the invention but is not intended to, and should not be construed to limit in any way the invention as set forth in the claims which follow thereafter.

EXPERIMENTAL DETAILS SECTION

EXAMPLE 1 – SYNTHESIS

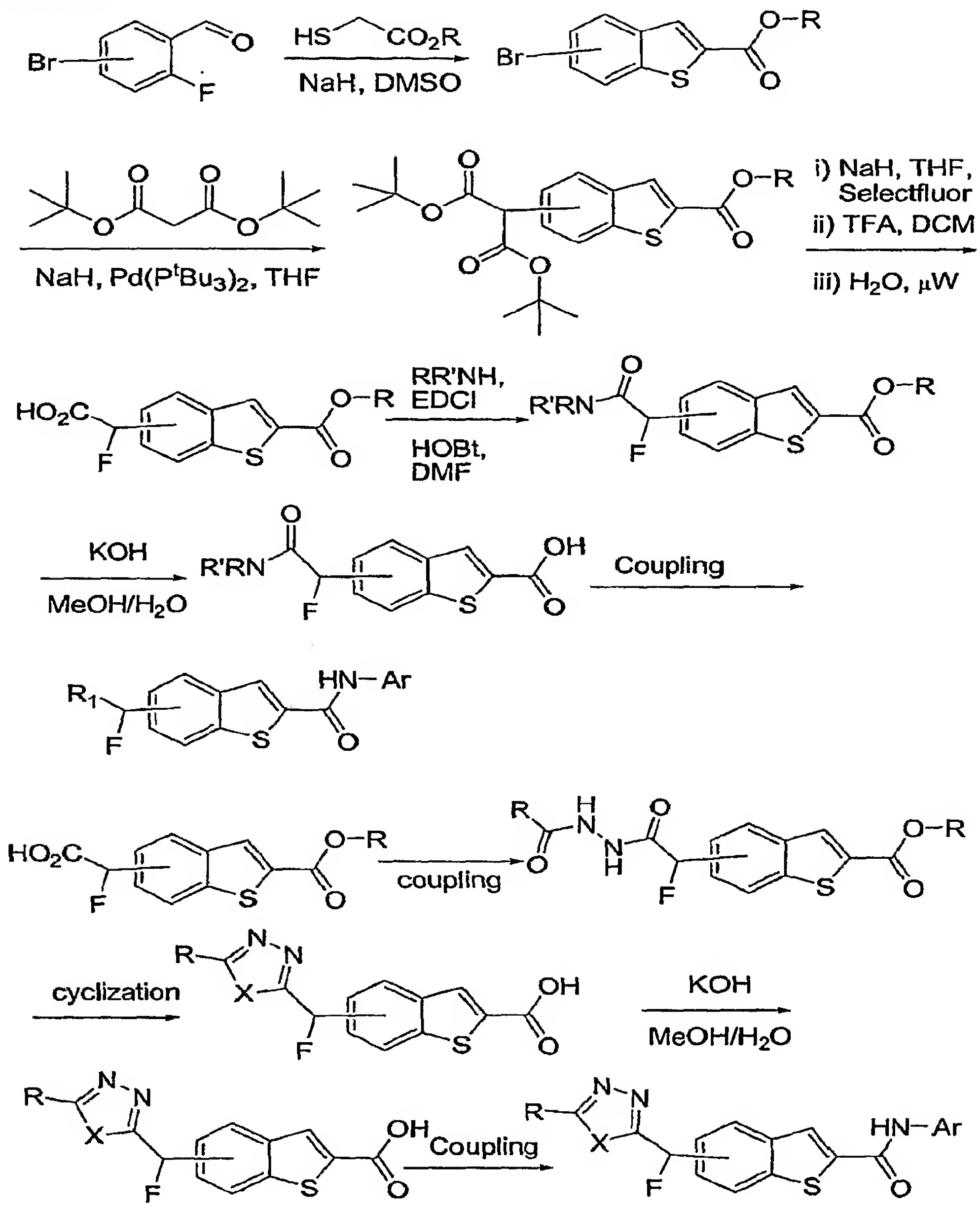
The compounds of the present invention were prepared by the general methods outlined in the synthetic schemes below, as exemplified below.

A. Benzothiophenes

A1. Compounds from (Carboxy-fluoro-methyl)-benzothiophenes.

Scheme 1 illustrates the use of (carboxy-fluoro-methyl)-benzothiophenes to generate amides, and various heterocycles.

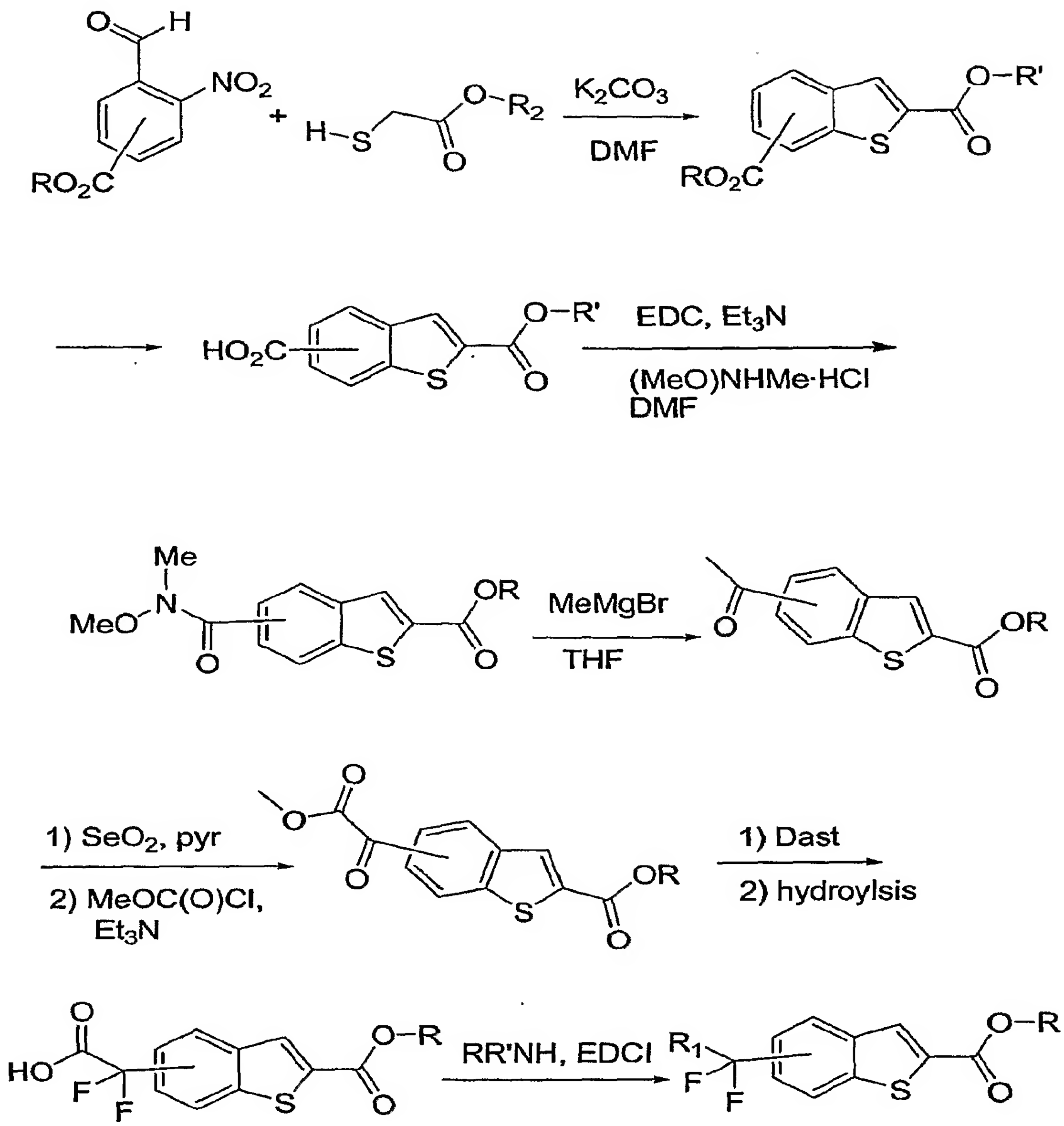
Scheme 1



A2. Compounds from (Carboxy-difluoro-methyl)-benzothiophenes.

Scheme 2 illustrates the use of (carboxy-difluoro-methyl)-benzothiophenes to generate amides, and various heterocycles.

Scheme 2

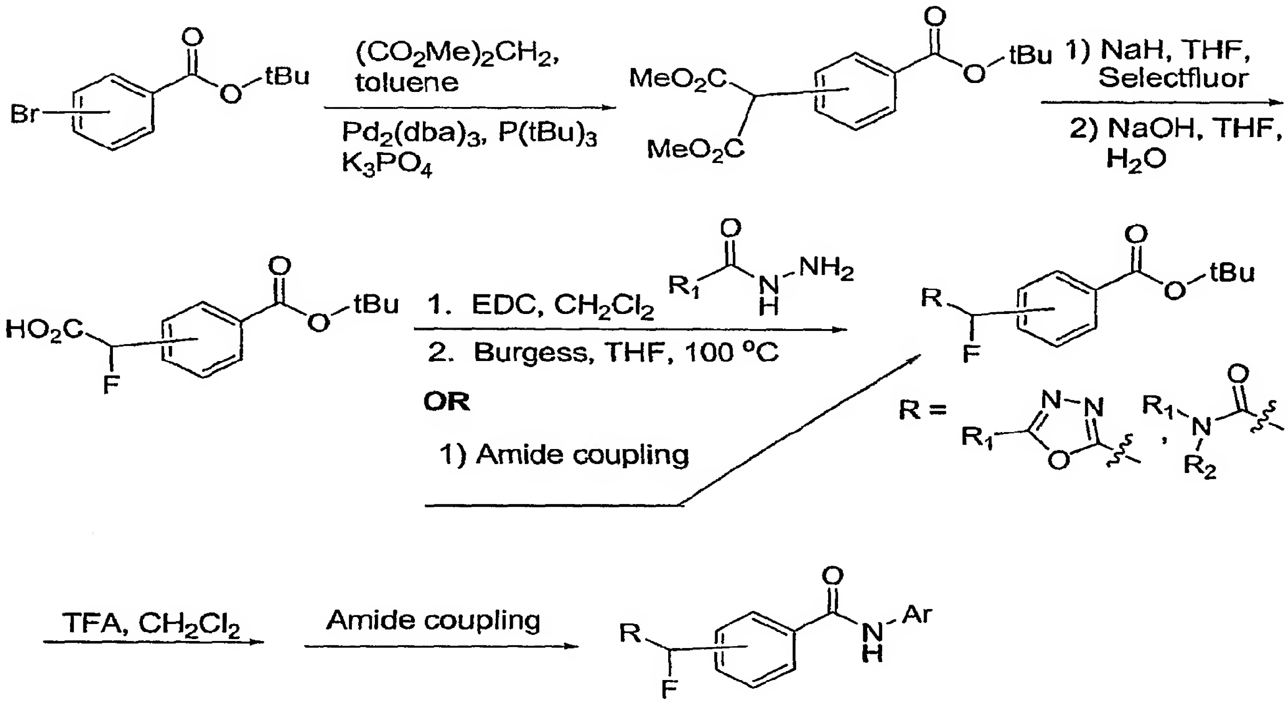


B. Benzamides

B1. Compounds from (Carboxy-fluoro-methyl)-benzoic acids.

Scheme 3 illustrates the use of (carboxy-fluoro-methyl)-benzoic acids to generate amides, and various heterocycles.

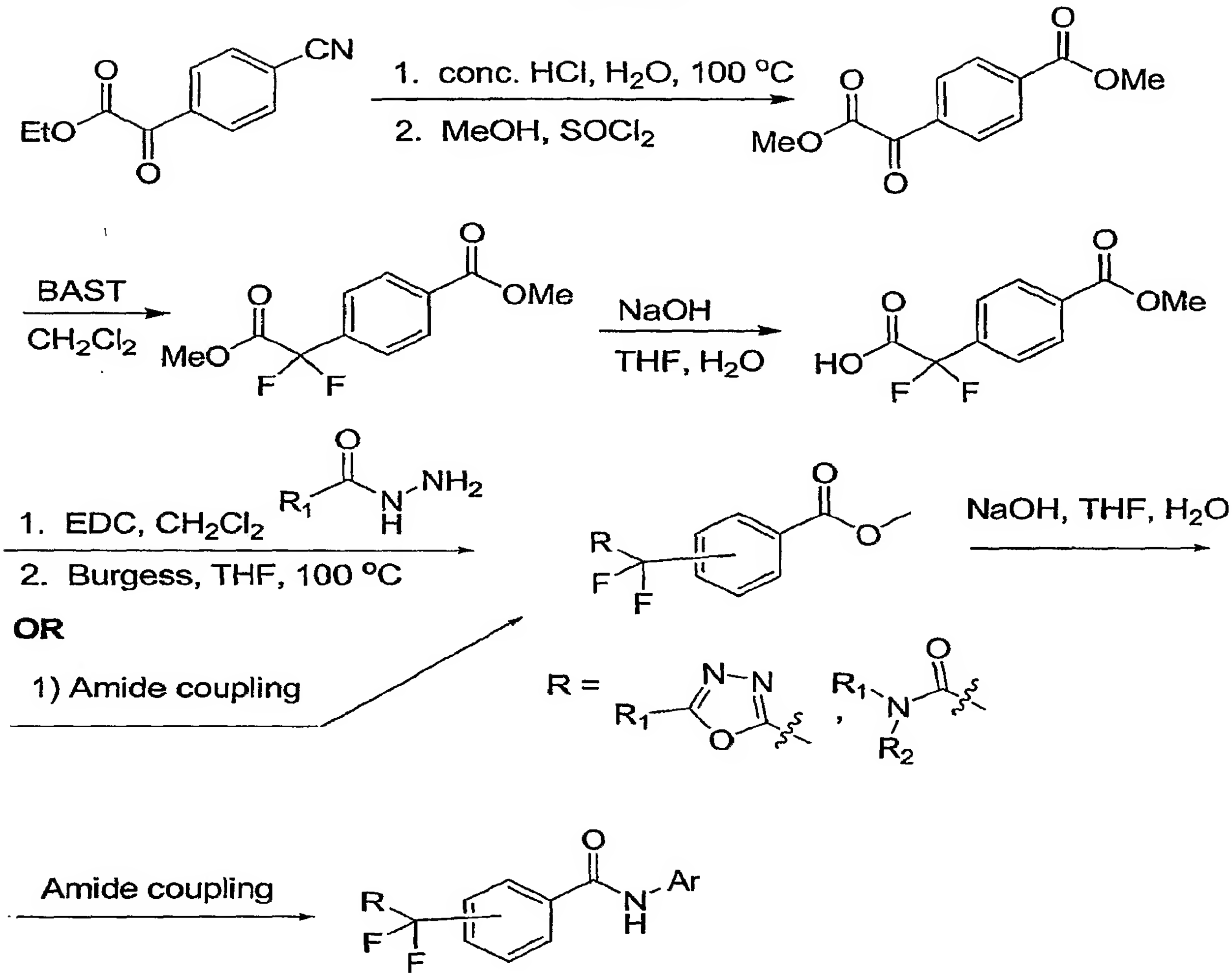
Scheme 3



B2. Compounds from (Carboxy-difluoro-methyl)-benzoic acids.

Scheme 4 illustrates the use of (carboxy-difluoro-methyl)-benzoic acids to generate amides, and various heterocycles.

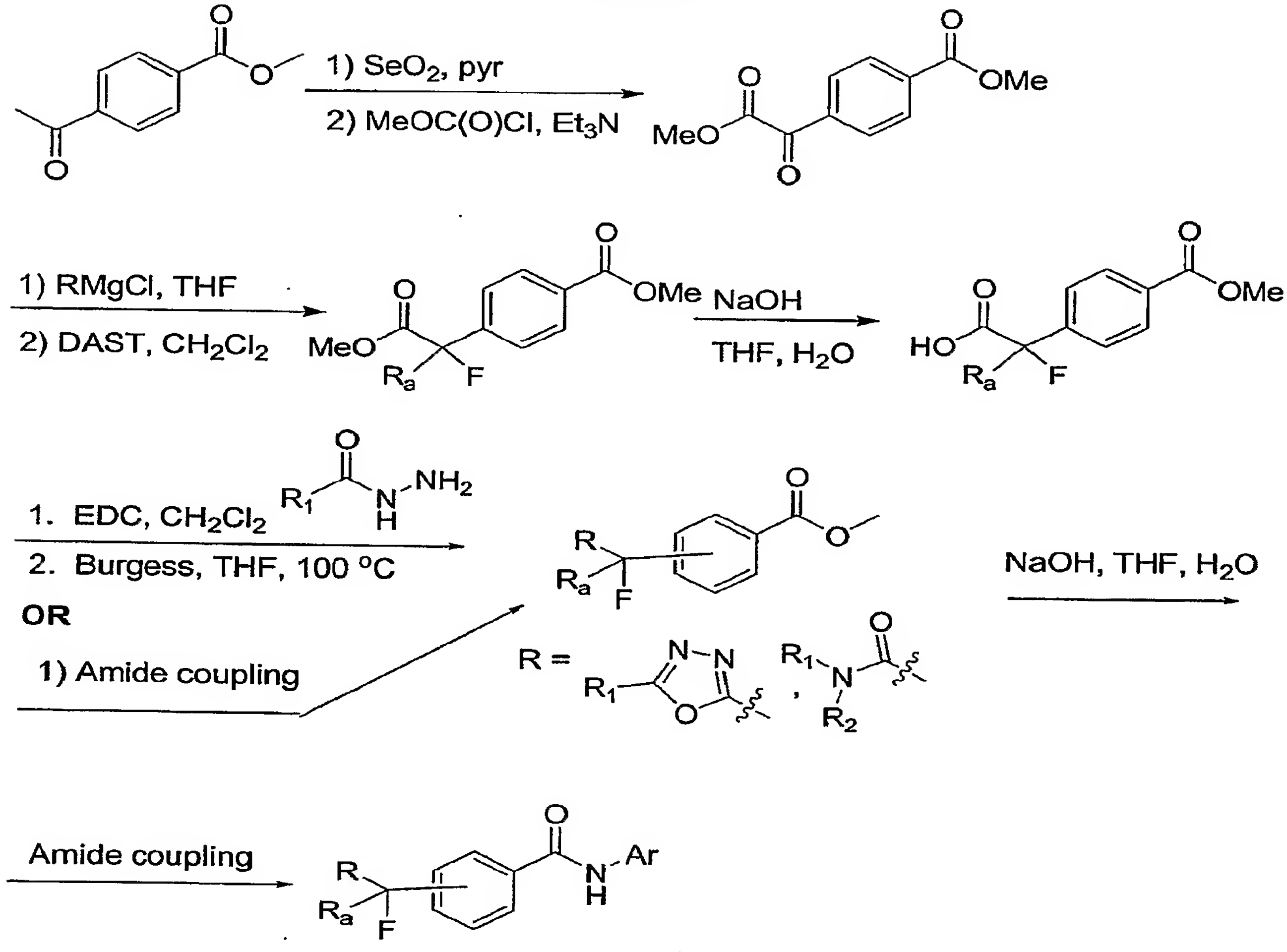
Scheme 4



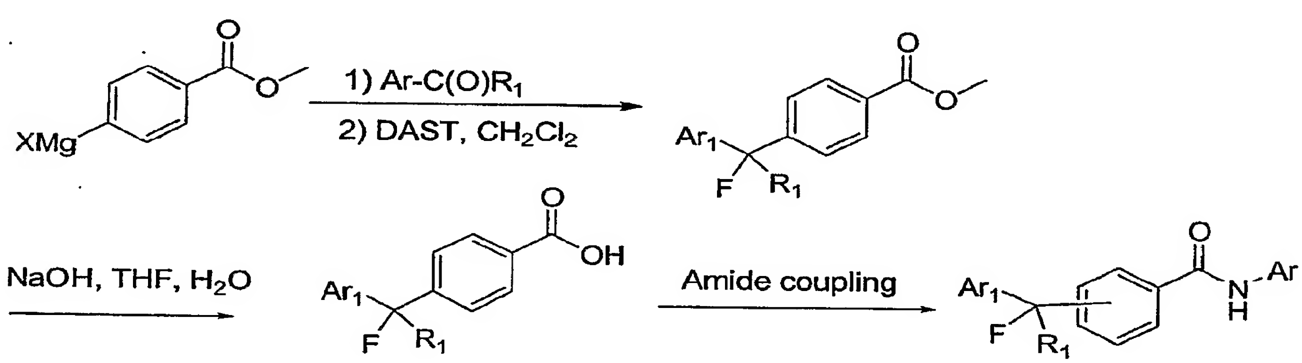
B3. Compounds from (Fluoro-alkoxycarbonyl-alkyl)-benzoic acids.

Scheme 5 illustrates the use of (fluoro-alkoxycarbonyl-alkyl)-benzoic acids to generate amides, and various heterocycles.

Scheme 5

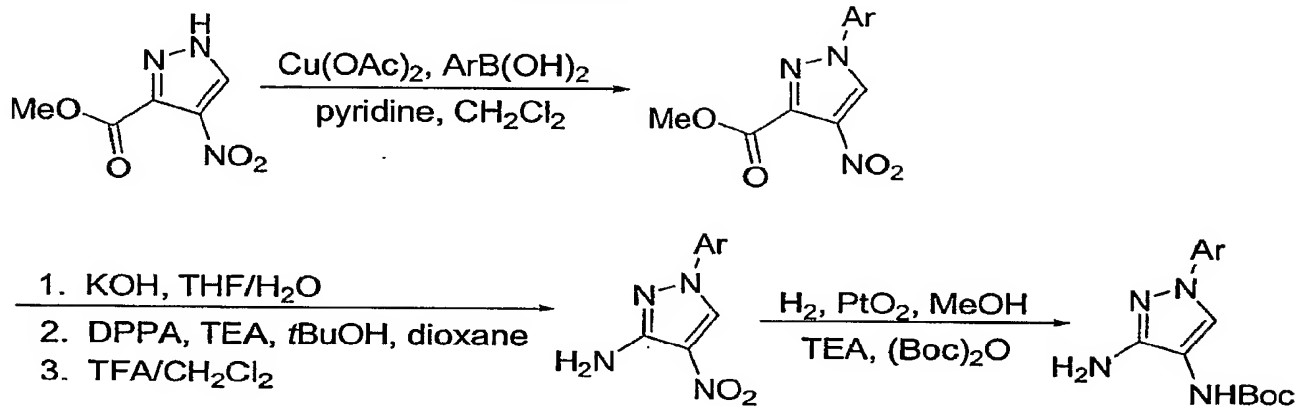


Scheme 8A

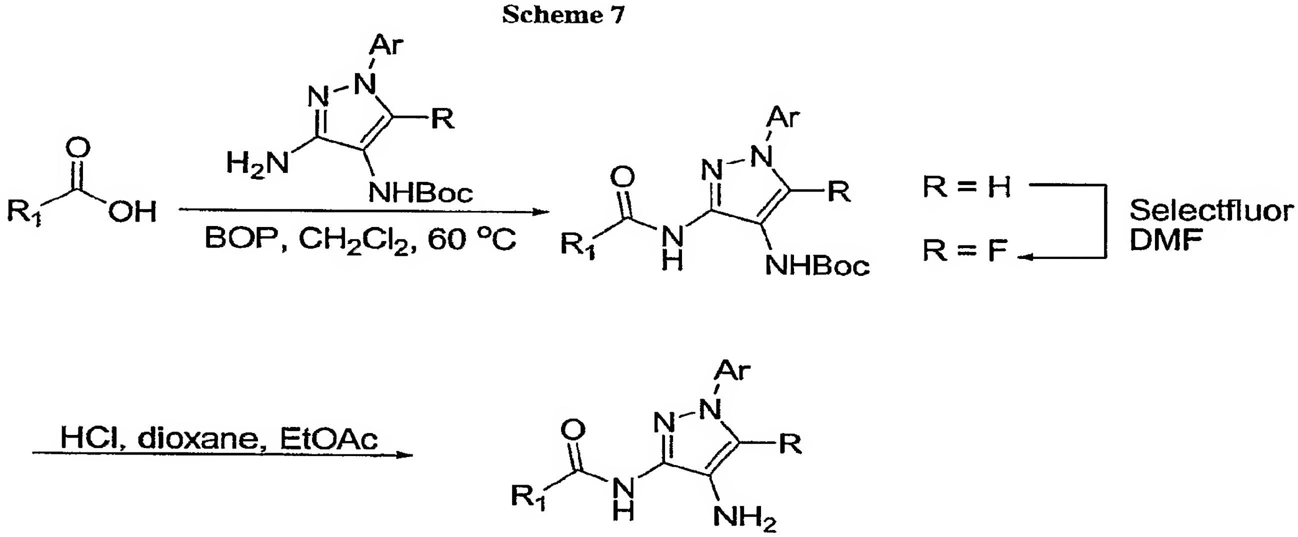


Synthesis of Diaminoarylpyrazole

Scheme 6

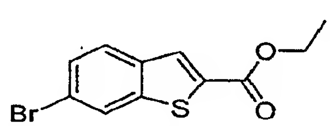


Scheme 7



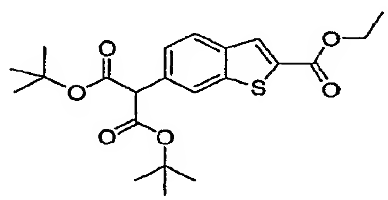
EXPERIMENTAL

Procedures for A1. Compounds from (carboxy-fluoro-methyl)-benzothiophenes.

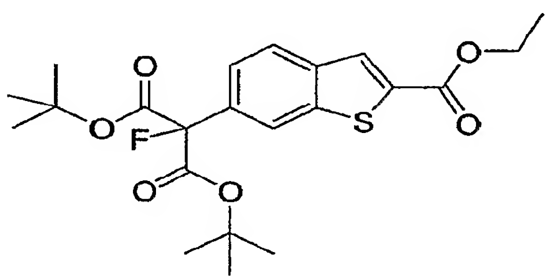


Ethyl 6-bromo-1-benzothiophene-2-carboxylate. Sodium hydride (60% dispersion in mineral oil, 0.73g, 18.3mmol) was suspended in DMSO (10mL) and ethyl mercaptoacetate (1.11mL, 10.1mmol) was added potionwise using a water bath to moderate the exotherm. On complete addition, the water bath was removed and stirring continued for 15 minutes. A solution of 4-bromo-2-fluorobenzaldehyde (1.86g, 9.16mmol) in DMSO (2mL) was added in one portion. The dark solution was stirred for 15 minutes before pouring into cold water (300mL). The products were extracted into Et_2O (2x200mL). The

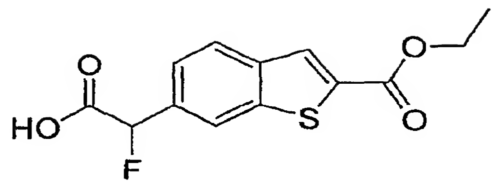
combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by MPLC gave the desired product (pale yellow solid). ^{1}H NMR (DMSO-d_6) δ 8.37 (d, J = 1.8 Hz, 1H), 8.17 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 8.4,1.8 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H).



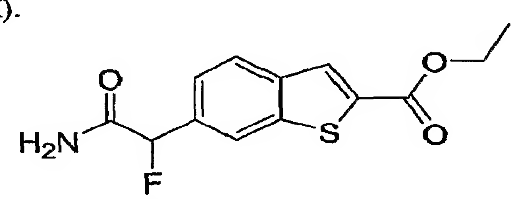
Di-*tert*-butyl [2-(ethoxycarbonyl)-1-benzothien-6-yl]malonate. Di-*tert*-butyl malonate (1.5g, 6.93mmol) was dissolved in THF (6mL) and sodium hydride (60%dispersion in mineral oil, 0.28g, 7.00mmol) was added. The mixture was stirred for 10 minutes before adding $Pd(P^tBu_3)_2$ (0.1g, 0.196mmol) and a solution of ethyl 6-bromo-1-benzothiophene-2-carboxylate (1.8g, 6.31mmol) in THF (12mL). The resulting mixture was heated to reflux under N_2 for 18 hours. Room temperature was attained, saturated NH_4Cl (150mL) was added and the products axtracted into EtOAc (2x125mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by MPLC gave the desired product (pale yellow solid). ^{1}H NMR (DMSO-d_6) δ 8.17 (s, 1H), 8.01 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.4,1.8 Hz, 1H), 4.83 (s, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.40 (s, 18H), 1.31 (t, J = 7.2 Hz, 3H).



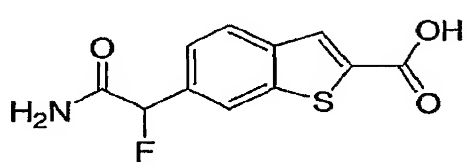
2-(2-Ethoxycarbonyl-benzo[b]thiophen-6-yl)-2-fluoro-malonic acid di-tert-butyl ester. To a suspension of sodium hydride (0.96 g, 24.0 mmol) in THF (75 mL) cooled to 0°C was added a solution of di-*tert*-butyl [2-(ethoxycarbonyl)-1-benzothien-6-yl]malonate (described above) (9.66 g, 23.0 mmol) in THF (150 mL) under nitrogen. The resulting orange solution was stirred at 4 °C for 15 minutes. DMF (225 mL) was added followed by Selectfluor (8.15 g, 23.0 mmol). The reaction was warmed to ambient temperature and stirred for 4 hours under nitrogen. The reaction was quenched with ammonium chloride solution and partitioned between ethyl acetate and water. The organics were washed with water and brine, dried over magnesium sulfate, filtered and evaporated *in vacuo*. Purification by flash column chromatography (2-20% ethyl acetate/hexanes) gave a mixture of starting material and product. This was resubjected to above reaction conditions and purified in a similar manner to give a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 8.17 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 9.1 Hz, 1H), 4.33 (q, J = 7.3 Hz, 2H), 1.44 (s, 18H), 1.31 (t, J = 7.0 Hz, 3H).



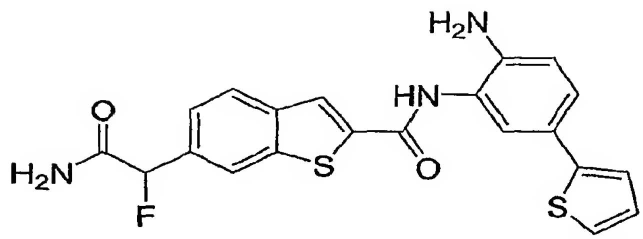
6-(Carboxy-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester. Di-*tert*-butyl [2-(ethoxycarbonyl)-1-benzothien-6-yl](fluoro)malonate (9.3 g) was stirred in DCM (40 mL)/TFA (20 mL) at room temperature overnight. The solvent was removed *in vacuo* and the residue partitioned between saturated $NaHCO_3$-EtOAc. The aqueous phase was acidified with 2N HCl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was suspended in H_2O (50mL) and heated to reflux for 2 hours. Room temperature was attained and the products extracted into EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the product as a pale yellow solid. ^1H NMR (DMSO-d_6) δ 13.60 (br s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 6.14 (d, J = 47.4 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H).



6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester. To a slurry of 6-(carboxy-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester (400 mg, 1.42 mmol) in DCM (10 mL) was added oxalyl chloride (0.148 mL, 1.70 mmol) and 2 drops of DMF. After 20 min, the resultant solution was added to a solution of NH_4OH (0.9 mL, 7.08 mmol) in DCM (5 mL) dropwise. After 1h, the solvent was removed *in vacuo* and the solid was triturated with MeOH and H_2O. The white solid was filtered and used without further purification. ^1H NMR (DMSO-d_6) δ 8.20 (s, 1H), 8.11 (s, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.91 (br s, 1H), 7.62 (br d, J = 2.4 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 5.94 (d, J = 45.7 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H). cal'd 282 (MH^+), exp 282 (MH^+).



6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid. To a solution of 6-(carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester (295 mg, 1.05 mmol) in MeOH/THF (1.5/6 mL) was added 1M LiOH (1.16 mL). The resultant solution was stirred overnight and 1N HCl was added dropwise to acidify (~2 mL). The solvent was removed *in vacuo* and the solid was used without further purification. cal'd 254 (MH^+), exp 254 (MH^+).

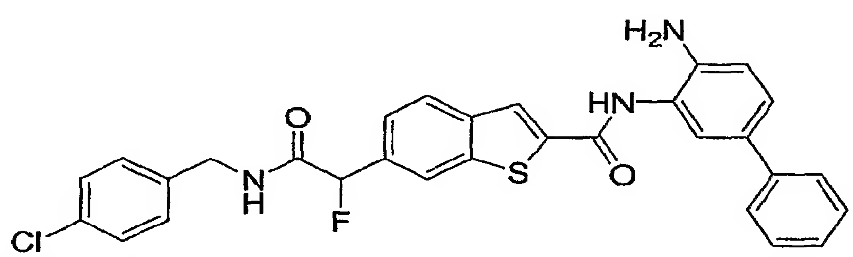


6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide.

Step 1: Coupling; To a solution of 6-(carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (100 mg, 0.40 mmol), (2-amino-4-thiophen-2-yl-phenyl)-carbamic acid tert-butyl ester (172 mg, 0.59 mmol) and N,N-diisopropylethylamine (0.103 mL, 0.59 mmol) in DMF (2.0 mL) was added (1*H*-1,2,3-benzotriazol-1-yloxy)(triisopropyl)phosphonium hexafluorophosphate (262 mg, 0.59 mmol) and the reaction was stirred overnight. The solvent was removed and the residue was purified by reverse phase chromatography (10-100% ACN/H_2O). The fractions were extracted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. ESIMS calcd 526 (M^+ + H), found 526 (M^+ + H).

Step 2: TFA Deprotection;

To a solution of (2-{[6-(carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carbonyl]-amino}-4-thiophen-2-yl-phenyl)-carbamic acid tert-butyl ester (163 mg, 0.31 mmol)) in methylene chloride (2 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at ambient temperature for 16 hours. The reaction was evaporated to dryness. The residue was washed with sat. $NaHCO_3$ and MeOH, and the solid was filtered. . ^{1}H NMR (DMSO-d_6) δ 10.03 (br s, 1H), 8.33 (s, 1H), 8.11 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.93 (s, 1H), 7.62 (br d, *J* = 2.4 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.33 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.29 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.23 (dd, *J* = 3.5, 1.8 Hz, 1H), 7.02 (dd, *J* = 5.2, 3.5 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 5.93 (d, *J* = 45.7 Hz, 1H), 5.24 (s, 2H). cal'd 427 (MH^+), exp 427 (MH^+).



6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide.

Step 1: Coupling; **6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid ethyl ester.** A solution of 6-(carboxy-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester (180 mg, 1.42 mmol), EDCI (134 mg, 0.70 mmol), HOBt (95 mg, 0.70 mmol) and 4-chlorobenzylamine (0.94 mL, 0.77 mmol) in DMF (4 mL) was stirred overnight. The solvent was removed. The residue was diluted with EtOAc, washed with H_2O, and $NaHCO_3$. The combined organic

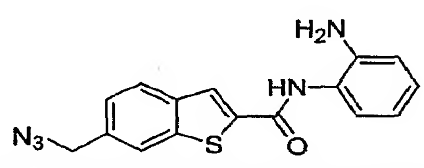
layers were dried over Na_2SO_4, filtered, concentrated yielded the crude amide, which was used without further purification. cal'd 406 (MH^+), exp 406 (MH^+).

Step 2: Hydrolysis; **6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid.** To a solution of 6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid ethyl ester (241 mg, 0.60 mmol) in MeOH/THF (2/3 mL) was added 2M NaOH (0.65 mL). The resultant solution was stirred overnight and 2N HCl was added dropwise to acidify (~0.7 mL). The solvent was removed *in vacuo* and the solid was used without further purification. cal'd 378 (MH^+), exp 378 (MH^+).

Step 3: Coupling; **[3-({6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carbonyl}-amino)-biphenyl-4-yl]-carbamic acid tert-butyl ester.** A solution of 6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (108 mg, 0.286 mmol), EDCI (74 mg, 0.383 mmol), HOBt (52 mg, 0.383 mmol) and (3-amino-biphenyl-4-yl)-carbamic acid tert-butyl ester (87 mg, 0.306 mmol) in DMF (4 mL) was stirred overnight. The solvent was removed. The residue was diluted with EtOAc, washed with H_2O, and $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered, concentrated yielded the crude amide, which was used without further purification. cal'd 378 (MH^+), exp 378 (MH^+).

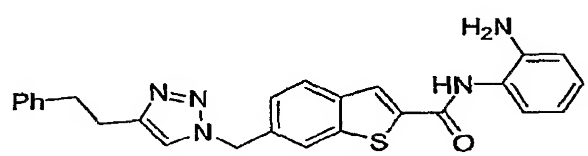
Step 4: TFA Deprotection; **6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide.** To a solution of [3-({6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carbonyl}-amino)-biphenyl-4-yl]-carbamic acid tert-butyl ester (164 mg, 0.26 mmol)) in methylene chloride (2 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at ambient temperature for 16 hours. The reaction was evaporated to dryness. The residue was washed with sat. $NaHCO_3$ and MeOH, and the solid was filtered. ^1H NMR (DMSO-d_6) δ 10.05 (br s, 1H), 9.12 (t, J = 5.0 Hz, 1H), 8.08 (br s, 1H), 8.00 (m, 1H), 7.55-7-51 (m, 3H), 7.49-7.45 (m, 1H), 7.38-7.33 (m, 5H), 7.33-7.27 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.21 (t, J = 6.9 Hz, 1H), 6.85-6.80 (m, 1H), 6.07 (d, J = 45.7 Hz, 1H), 5.15 (s, 2H), 4,33-4.26 (m, 2H). cal'd 545 (MH^+), exp 545 (MH^+).

Compounds from 5- and 6-azidomethylbenzothiophenes.



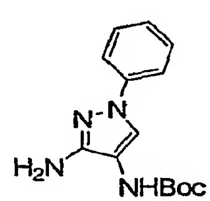
***N*-(2-aminophenyl)-6-(azidomethyl)-1-benzothiophene-2-carboxamide.** 6-Hydroxymethyl-benzo[b]thiophene-2-carboxylic acid ethyl ester (500 mg, 2.12 mmol) was dissolved in CH_2Cl_2 (10 mL) and Et_3N (443 mL, 3.18 mmol) followed by mesyl chloride (197 mL, 2.54 mmol) were added. The solution was allowed to stir for 30 min and the solution was poured into 50 mL of Et_2O. The organic solution was washed with 50 mL of 1 M $KHSO_4$ followed by 50 mL of brine. The solution was dried over $MgSO_4$ and the crude mesylate was used without further purification. This mesylate was dissolved in DMF (5 mL) and NaN_3 (325 mg, 5.00 mmol) was added. The suspension was allowed to stir for 30 min then poured into 50 mL of water and 50 mL of EtOAc. The layers were separated then the organic

solution was washed with 50 mL of brine and dried over $MgSO_4$. The solution was concentrated to give the crude azide, which was used without further purification. The azide was dissolved in 8.80 mL of THF and 2.20 mL of MeOH and 2.20 mL of a 1 M solution of LiOH (2.20 mmol) was added. The solution was allowed to stir for 18 h, then diluted with 50 mL of EtOAc and washed with 50 mL of 1M $KHSO_4$ followed by 50 mL of brine. The organic layer was dried and concentrated to give the crude acid that was used without further purification. This acid was dissolved in 4 mL of DMF. 1,2-phenylenediamine (459 mg, 4.24 mmol), EDC (810 mg, 4.24 mmol), and HOBT (573 mg, 4.24 mmol) were added and the solution was allowed to stir for 2 h. The solution was diluted with 50 mL of EtOAc and washed with 50 mL of water and 50 mL of brine. The organic solution was dried and concentrated then purified by flash chromatography (12-100% EtOAc in hexanes) to give the amide as a light yellow powder. ^1H NMR (600 MHz, $CDCl_3$) δ 4.49 (s, 2), 6.85 (t, 2, J = 6.1), 7.10 (t, 1, J = 7.4), 7.37 (t, 2, J = 8.5), 7.82 (s, 1), 7.85 (d, 1, J = 8.2), 7.90 (m, 2). MS cal'd 324 (MH^+), exp 324 (MH^+).



***N*-(2-aminophenyl)-6-{[4-(2-phenylethyl)-1*H*-1,2,3-triazol-1-yl]methyl}-1-benzothiophene-2-carboxamide.** $CuSO_4$ (16 µL of 7.5 % w/v sol'n, 0.0075 mmol) was added to a solution of *N*-(2-aminophenyl)-6-(azidomethyl)-1-benzothiophene-2-carboxamide (32 mg, 0.10 mmol) and 4-phenyl-1-butyne (16.8 µL, 0.120 mmol) in MeOH. Sodium ascorbate (20 µL of a 1 M sol'n, 0.020 mmol) was added followed by Ph_3P (5.9 mg, 0.023 mmol). The solution was allowed to stir overnight then the solution was directly purified by reverse phase HPLC to give the trazole as a light yellow powder. ^1H NMR (600 MHz, $CDCl_3$) δ 2.95-2.97 (m, 2), 3.00-3.01 (m, 2), 5.58 (s, 2), 6.84-6.86 (m, 2), 7.06 (s, 1), 7.10-7.12 (m, 3) 7.15 (t, 1, J = 7.4), 7.20-7.23 (m, 3), 7.39 (d, 1, J = 7.0), 7.66 (s, 1), 7.80 (d, 1, J = 8.2), 7.88 (s, 1), 7.95 (s, 1). MS cal'd 454 (MH^+), exp 454 (MH^+).

Synthesis of Diaminoarylpyrazoles.



***tert*-butyl (3-amino-1-phenyl-1*H*-pyrazol-4-yl)carbamate.**

Step A: Copper Coupling

A solution of methyl 4-nitro-1*H*-pyrazole-3-carboxylate (54.0g, 315.6 mmol), phenylboronic acid (77.0g, 631.2 mmol), copper(II) acetate (86.0g, 473.4 mmol) and pyridine (49.9g, 631.2 mmol) in methylene chloride (600 mL) was stirred at ambient temperature open to air for 48 hours. The reaction was evaporated *in vacuo*, diluted with 1000mL methylene chloride and filtered through a large plug of silica (washing with 2 liters methylene chloride). The solvent was evaporated *in vacuo*. ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.73 (m, 2H), 7.50 (m, 3H), 4.02 (s, 3H).

Step B: Saponification

A solution of methyl 4-nitro-1-phenyl-1*H*-pyrazole-3-carboxylate (78.1g, 315.9 mmol) in THF (600 mL) was treated with 4M potassium hydroxide (79mL, 316 mmol) dropwise and the solution was stirred at ambient temperature for 16 hours. The reaction was evaporated *in vacuo* and acidified with 6M HCl. After addition of water (500 mL) the solids were filtered off and dried to give 72.1g (97%, 2 steps) of desired compound as a grayish solid. ^{1}H NMR (CD_3OD) δ 9.37 (bs, 1H), 7.88 (m, 2H), 7.59 (m, 2H), 7.44 (m, 1H).

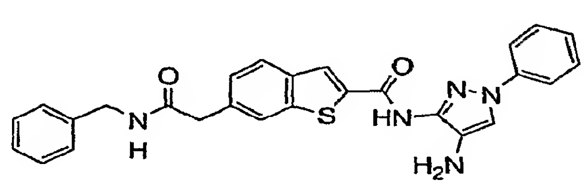
Step C: Curtius

A solution of 4-nitro-1-phenyl-1*H*-pyrazole-3-carboxylic acid (20.0g, 85.8 mmol), triethylamine (36.0mL, 257.3 mmol), and diphenylphosphoryl azide (37.8g, 137.2 mmol) in dioxane (400 mL) and *tert*-butanol (200 mL) was heated to reflux for 16 hours. The reaction was evaporated to dryness *in vacuo*, diluted with methylene chloride (400 mL) and treated with trifluoroacetic acid (128g, 857.7 mmol). The solution was stirred at ambient temperature for 16 hours. The reaction was evaporated *in vacuo* and the resulting oil diluted with hexanes (750 mL), ethyl acetate (150 mL) and methylene chloride (100 mL). The solids were filtered, washed with above solvent system (hexanes:ethyl acetate;methylene chloride 75:15:10), and dried to give 12.0g of desired product as yellow solid. ^{1}H NMR ($CDCl_3$) δ 8.43 (s, 1H), 7.62 (m, 2H), 7.48 (m, 2H), 7.37 (m, 1H).

Step D: Hydrogenation/Boc protection

A solution of 4-nitro-1-phenyl-1*H*-pyrazol-3-amine (0.15g, 0.74 mmol), di-tertbutyl dicarbonate (0.16g, 0.74 mmol), triethylamine (0.19g, 1.84 mmol) in methanol 20 mL was degassed with nitrogen and treated with platinum oxide (17mg, 10 mol%). The solution was placed under a hydrogen atmosphere and stirred at ambient temperature for 2 hours. The reaction was then degassed with nitrogen, filtered through celite, washed with methanol and evaporated *in vacuo*. Flash chromatography (20-35% ethyl acetate/hexanes) gave 0.109g (54%) of title compound as a purplish solid. ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.51 (m, 2H), 7.37 (m, 2H), 7.18 (m, 1H), 6.40 (bs, 1H).

General Procedure for Coupling of Diaminoarylpyrazoles.



***N*-(4-amino-1-phenyl-1*H*-pyrazol-3-yl)-6-[2-(benzylamino)-2-oxoethyl]-1-benzothiophene-2-carboxamide.**

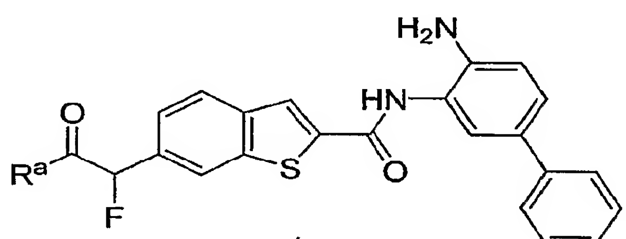
Step A: Bop coupling

To a solution of 6-[2-(benzylamino)-2-oxoethyl]-1-benzothiophene-2-carboxylic acid (0.25g, 0.77 mmol), *tert*-butyl (3-amino-1-phenyl-1*H*-pyrazol-4-yl)carbamate (0.26g, 0.96 mmol) and N,N-diisopropylethylamine (0.15g, 1.15 mmol) in methylene chloride (5 mL) was added (1*H*-1,2,3-benzotriazol-1-yloxy)(triisopropyl)phosphonium hexafluorophosphate (0.51g, 1.15 mmol). The reaction was sealed and heated to 60 °C for 16 hours. The reaction was purified by flash chromatography (0-2.5% methanol/methylene chloride) to give crude product. ESIMS calcd 582.2 (M^+ + H), found 582.2 (M^+ + H).

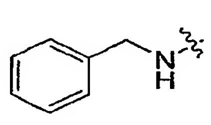
Step B: Deprotection

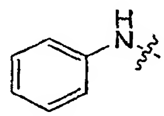
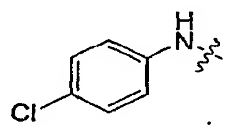
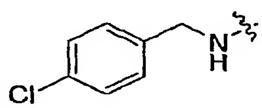
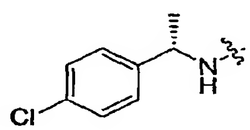
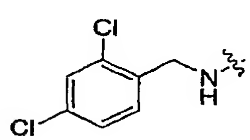
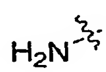
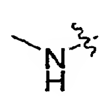
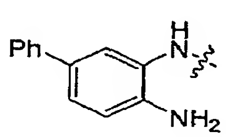
To a solution of crude *tert*-butyl {3-[({6-[2-(benzylamino)-2-oxoethyl]-1-benzothien-2-yl}carbonyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate (from step A) in ethyl aceate (10 mL) and methanol (10 mL) was added 4M HCl in dioxane (10 mL) and the resulting solution was stirred for 16 hours at ambient temperature. The reaction was evaporated to dryness and purified by reverse phase LC to give 148mg (40%, 2 steps) of *N*-(4-amino-1-phenyl-1*H*-pyrazol-3-yl)-6-[2-(benzylamino)-2-oxoethyl]-1-benzothiophene-2-carboxamide as a white solid. ^{1}H NMR (DMSO-d_6) δ 11.01 (s, 1H), 8.59 (t, J = 5.87 Hz, 1H), 8.35 (s, 1H), 7.89 (t, J = 3.82 Hz, 2H), 7.80 (s, 1H), 7.67 (d, J = 7.92 Hz, 2H), 7.42 (t, J = 7.33 Hz, 2H), 7.36 (d, J = 9.1 Hz, 1H), 7.28 (t, J = 7.92 Hz, 2H), 7.19 (m, 4H), 4.25 (d, J = 5.87 Hz, 2H), 3.61 (s, 2H). ESIMS calcd 482.2 (M^+ + H), found 482.1 (M^+ + H).

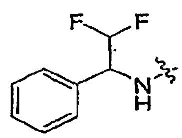
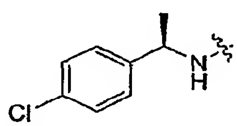
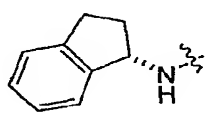
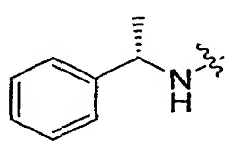
Additional α-aminoaryl analogs were prepared in procedures similar to those described for the preparations of the above examples. Unless otherwise indicated, the compounds were isolated as the free form (parent).

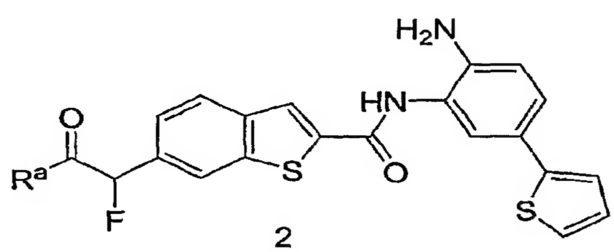


1

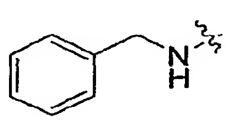
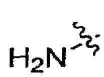
Cpd#	R^a	Name	MS
1-1		6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 510 (MH^+), 510 (MH^+)

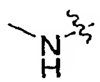
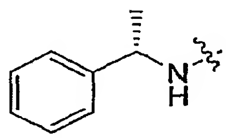
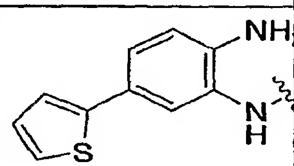
1-2		6-(Fluoro-phenylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 496 (MH^+), exp 496 (MH^+)
1-3		6-[(4-Chloro-phenylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 531 (MH^+), exp 531 (MH^+)
1-4		6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 545 (MH^+), exp 545 (MH^+)
1-5		6-{[1-(*S*)-(4-Chloro-phenyl)-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 558, 560 (MH^+), 558, 560 (MH^+)
1-6		6-[(2,4-Dichloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 579 (MH^+), exp 579 (MH^+)
1-7		6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 420 (MH^+), exp 420 (MH^+)
1-8		6-(Fluoro-methylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 434 (MH^+), exp 434 (MH^+)
1-9		6-[(4-Amino-biphenyl-3-ylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 587 (MH^+), exp 587 (MH^+)

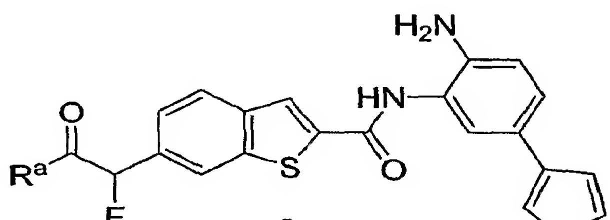
1-10		6-[(2,2-Difluoro-1-phenyl-ethylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 560 (MH^+), exp 560 (MH^+)
1-11		6-{[1-(*R*)-(4-Chloro-phenyl)-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 558, 560 (MH^+), 558, 560 (MH^+)
1-12		6-[Fluoro-(indan-1-(*S*)-ylcarbamoyl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide	cal'd 536 (MH^+), 536 (MH^+)
1-13		6-{[1-(*S*)-Phenyl-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide; isolated as the TFA salt	cal'd 524 (MH^+), 524 (MH^+)



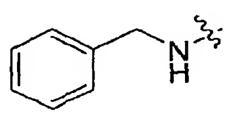
2

Cpd #	R^a	Name	MS
2-1		6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 516 (MH^+), 516 (MH^+)
2-2		6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 426 (MH^+), exp 426 (MH^+)

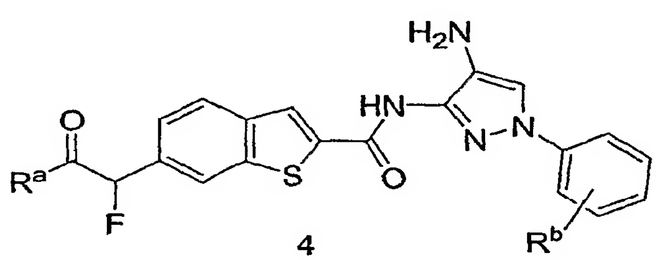
2-3		6-(Fluoro-methylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 440 (MH^+), exp 440 (MH^+)
2-4		6-[Fluoro-(1-(*S*)-phenyl-ethylcarbamoyl)-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 530 (MH^+), 530 (MH^+)
2-5		6-[(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 599 (MH^+), exp 599 (MH^+)



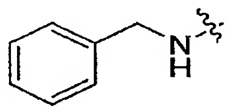
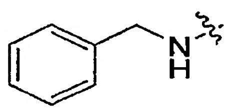
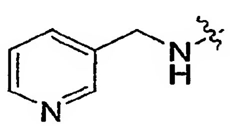
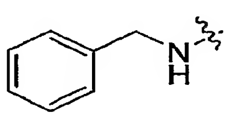
3

Cpd#	R^a	Name	MS
3-1		6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide; isolated as the TFA salt	cal'd 516 (MH^+), 516 (MH^+)

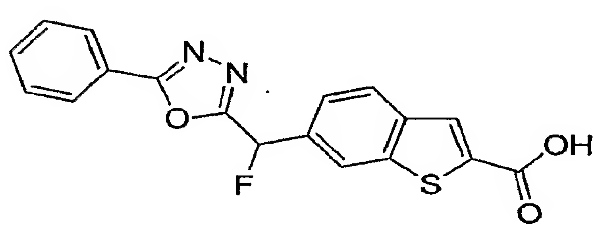
Additional α-aminopyrazole analogs were prepared in procedures similar to those described for the preparation of the above *N*-(4-amino-1-phenyl-1*H*-pyrazol-3-yl)-6-[2-(benzylamino)-2-oxoethyl]-1-benzothiophene-2-carboxamide.



4

Cpd #	R^a	R^b	Name	MS
4-1		3-Cl	6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide; isolated as the TFA salt	cal'd 534.1 (MH^+), 534.0(MH^+)
4-2		3-Cl	6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide	cal'd 534.1 (MH^+), exp 534.1(MH^+)
4-3	H_2N-	H	6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide	cal'd 410 (MH^+), exp 410 (MH^+)
4-4		H	6-{Fluoro-[(pyridin-3-ylmethyl)-carbamoyl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide; isolated as the HCl salt	cal'd 501.1(MH^+), exp 501.1 (MH^+)
4-5		H	N-(4-amino-1-phenyl-1H-pyrazol-3-yl)-6-[2-(benzylamino)-1-fluoro-2-oxoethyl]-1-benzothiophene-2-carboxamide	cal'd 500 (MH^+), exp 500 (MH^+)

Oxadiazoles

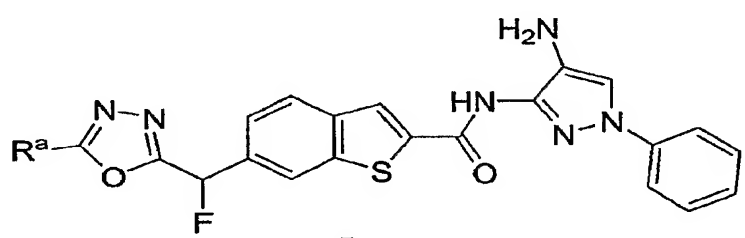


6-[Fluoro(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1-benzothiophene-2-carboxylic acid.

Step A: EDC Coupling; **6-[2-(N'-Benzoyl-hydrazino)-1-fluoro-2-oxo-ethyl]-benzo[b]thiophene-2-carboxylic acid ethyl ester.** A solution of [2-(ethoxycarbonyl)-1-benzothien-6-yl](fluoro)acetic acid (50 mg, 0.18 mmol) and benzohydrazide (36.2 mg, 0.27 mmol) in methylene chloride (2 mL) was treated with EDC (51 mg, 0.27 mmol) and the resulting solution was stirred at ambient temperature for 3 hours. The reaction was purified by flash chromatography (1-5% methanol/methylene chloride) to give ethyl 6-[2-(2-benzoylhydrazino)-1-fluoro-2-oxoethyl]-1-benzothiophene-2-carboxylate as a white solid. ESIMS calcd 401.1 ($M^+ + H$), found 401.0 ($M^+ + H$).

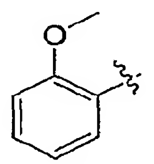
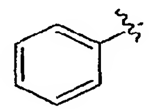
Step B: Dehydration/Saponification; **6-[Fluoro-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid.** A solution of ethyl 6-[2-(2-benzoylhydrazino)-1-fluoro-2-oxoethyl]-1-benzothiophene-2-carboxylate (51 mg, 0.13 mmol) in THF (2.0 mL) was treated with Burgess reagent (45 mg, 0.19 mmol). The reaction vessel was sealed and heated to 120°C in the microwave reactor for 20 minutes. The reaction was evaporated in vacuo and purified by flash chromatography (10-40% ethyl acetate/hexanes) to give ethyl 6-[fluoro(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1-benzothiophene-2-carboxylate as a white solid. ESIMS calcd 383.1 ($M^+ + H$), found 383.0 ($M^+ + H$). To a solution of ethyl 6-[fluoro(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1-benzothiophene-2-carboxylate in THF (2.5 mL) was added 1M sodium hydroxide (5.0 mL, 5.0 mmol) and the resulting solution was stirred at ambient temperature for 1 hour. The reaction was partitioned between ethyl acetate and 1M HCl solution. The organics were dried over sodium sulfate, filtered and evaporated to give 6-[fluoro(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1-benzothiophene-2-carboxylic acid as a white solid. ESIMS calcd 355.1 ($M^+ + H$), found 355.0 ($M^+ + H$).

α-aminoaryl analogs from the carboxylic acids were prepared in procedures similar to those described for the preparations of the above examples. All of the compounds were isolated as the TFA salt.

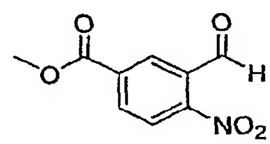


5

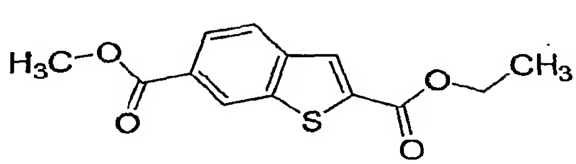
Cpd #	R^a	Name	MS
5-1	Me	6-[Fluoro-(5-methyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide	cal'd 449.1 (MH^+), exp 449.1 (MH^+)

5-2		6-{Fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide	cal'd 541.1 (MH^+), 541.1 (MH^+)
5-3		6-[Fluoro-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide	cal'd 511.1 (MH^+), 511.1 (MH^+)

__Procedures for A2. Compounds from (carboxy-difluoro-methyl)-benzothiophenes.__

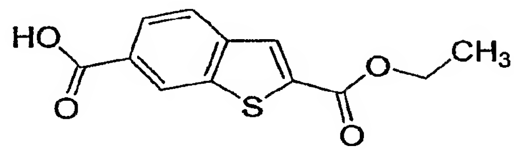


3-Formyl-4-nitro-benzoic acid methyl ester. A solution of 3-methyl-4-nitro-benzoic acid methyl ester (24.99 g, 128.1 mmol) and N,N-dimethylformamide dimethyl acetal (40.0 mL, 300 mmol) was heated at 140°C for 22.5 h. After cooling to rt, the reaction mixture was concentrated and the residue was crystallized from MeOH to give a purple solid. This solid was dissolved in THF (500 mL) and water (500 mL), and sodium periodate (62.62 g, 292.8 mmol) was added followed by additional sodium periodate (15.6 g, 72.9 mmol) two hours later. After stirring at rt for an additional 1 h, the reaction mixture was filtered through Celite washing with EtOAc (2 L). The filtrate was washed with saturated $NaHCO_3$ (600 mL) and the organic layer was dried over Na_2SO4. After filtration, the filtrate was concentrated and the residue was passed through a pad of silica gel, washing with CH_2Cl_2/hexanes (75%-100%). The filtrate was concentrated and dried to give 3-formyl-4-nitro-benzoic acid methyl ester as yellowish solid. MS (EI): cal'd 210.0 (MH^+), exp 210.2 (MH^+).

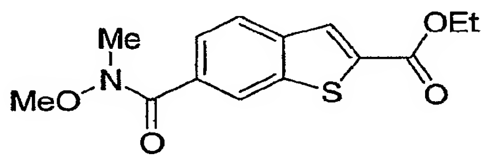


Benzo[b]thiophene-2,6-dicarboxylic acid 2-ethyl ester 6-methyl ester. A mixture of 4-formyl-3-nitro-benzoic acid methyl ester (15.2 g, 72.8 mmol), mercapto-acetic acid ethyl ester (8.70 mL, 79.3 mmol) and K_2CO_3 (12.9 g, 93.1 mmol) in 140 mL of anhydrous DMF was heated at 50°C overnight. After cooling to rt, the mixture was poured into 1 L of ice-water and the resulting mixture was stirred for 40min. The solid formed was filtered and washed with 4×70 mL of water. After drying, benzo[b]thiophene-2,6-

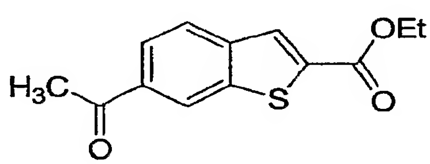
dicarboxylic acid 2-ethyl ester 6-methyl ester was obtained as a pale solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.56 (s, 1H), 8.09-7.97 (m, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 3.95 (s, 3H), 1.40 (t, *J* = 6.8 Hz, 3H). MS (EI): cal'd 265.0 (MH^+), exp 265.0 (MH^+).



Benzo[b]thiophene-2,6-dicarboxylic acid 2-ethyl ester. A mixture of benzo[b]thiophene-2,6-dicarboxylic acid 2-ethyl ester 6-methyl ester (14.9 g, 56.4 mmol) and LiI (38.0 g, 284 mmol) in 120 mL of anhydrous pyridine was refluxed for 3 h. After cooling to rt, the mixture was poured into ice-cold 2N HCl (800 mL). The solid formed was filtered and washed with 3 × 100 mL of water. After drying, the solid was crystallized from MeOH to give benzo[b]thiophene-2,6-dicarboxylic acid 2-ethyl ester as a pale solid. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.66 (s, 1H), 8.21 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.96 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.40 (t, *J* = 6.8 Hz, 3H). MS (EI): cal'd 251.0 (MH^+), exp 251.1 (MH^+).

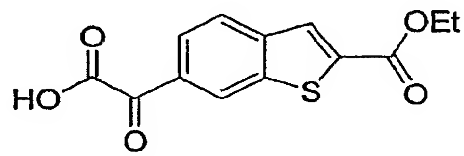


Ethyl 6-{[methoxy(methyl)amino]carbonyl}-1-benzothiophene-2-carboxylate. 2-(ethoxycarbonyl)-1-benzothiophene-6-carboxylic acid (2.5 g, 10.0 mmol) was dissolved in DMF (20mL) and cooled to 0°C. EDCI (1.92 g, 10.0 mmol) was added to the reaction followed by (MeO)NHMe·HCl (1.5 g, 15.0 mmol) and then Et_3N (1.4 mL, 10.0 mmol). The reaction was allowed to stir for 1 h at 0°C. Water was added to reaction mixture and then extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, concentrated yielded the crude amide. Purification by flash column chromatography provided the desired amide. ^{1}H NMR (CDCl3, 600 MHz) δ 8.20 (s, 1H), 8.04 (s, 1H), 7.87 (d, *J*= 8.4 Hz, 1H), 7.69 (dd, *J* = 8.4, 1.0 Hz, 1H), 4.39 (d, *J* = 7.2 Hz, 2H), 3.54 (s, 3H), 3.38 (s, 3H), 1.4 (t, *J* = 7.2 Hz, 3H). MS: cal'd (MH^+) 294, exp (MH^+) 294.

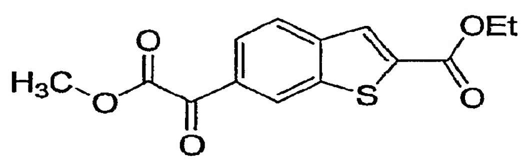


Ethyl 6-acetyl-1-benzothiophene-2-carboxylate. To a solution of ethyl 6-{[methoxy(methyl)amino]carbonyl}-1-benzothiophene-2-carboxylate (0.07 g, 0.22 mmol) in THF (3 mL) at -78°C was added MeLi (0.15 mL, 1.6 M in Et_2O, 0.24 mmol). The reaction was stirred for 1 h at -78°C before saturated ammonium chloride solution was added to quench the reaction. At which time the

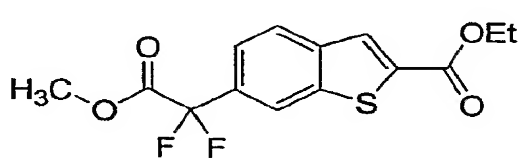
reaction mixture was allowed to warm to room temperature and then extracted with a mixture of hexane:ethyl acetate solution (3:1) (3x). The combined organic layers was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was chromatographed to provide the ketone. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.46 (s, 1H), 8.07 (s, 1H), 7.98 (dd, J = 8.2, 1.2 Hz, 1H), 7.92 (m, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.69 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H). MS: cal'd (MH^+) 249, exp (MH^+) 249.



6-Carboxyoxalyl-benzo[b]thiophene-2-carboxylic acid ethyl ester. To solution of ethyl 6-acetyl-1-benzothiophene-2-carboxylate (1.0 g, 40.3 mmol) in pyridine (4 mL) at 90°C was added selenium dioxide (782 mg, 7.05 mmol) portionwise over 1.5h. After 7 h, cooled to RT and filtered via Celite. The solvent was removed *in vacuo* and the residue was diluted with EtOAc, washed with 0.5N HCl, dried (MgSO4) and the solvent was evaporated under reduced pressure. The material was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.45 (br s, 1H), 8.22 (br s, 1H), 8.05 (d, J = 8.2 Hz, 1H), 7.84 (dd, J = 8.2, 1.5 Hz, 1H), 4.34 (q, J = 7.3 Hz, 2H), 1.32 (t, J = 7.3 Hz, 3H). cal'd 279 (MH^+), exp 279 (MH^+).

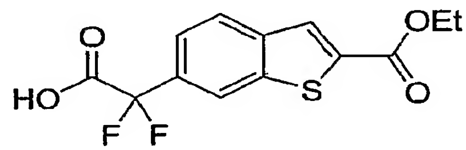


6-Methoxyoxalyl-benzo[b]thiophene-2-carboxylic acid ethyl ester. To a solution of 6-oxalyl-benzo[b]thiophene-2-carboxylic acid ethyl ester (500 mg, 1.80 mmol) and triethylamine (0.250 mL, 1.80 mmol) in CH_2Cl_2 (5 ml) at RT was added methyl chloroformate (0.139 ml, 1.80 mmol). After 30 min, the reaction mixture was diluted with CH_2Cl_2 (5 ml) and washed with H_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Biotage 25M), eluting with EtOAc/hexane to givea yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.59 (br s, 1H), 8.09 (br s, 1H), 8.03 (dd, J = 8.2, 1.5 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H), 4.42 (q, J = 7.3 Hz, 2H), 4.02 (s, 3H), 1.41 (t, J = 7.3 Hz, 3H). cal'd 293 (MH^+), exp 293 (MH^+).



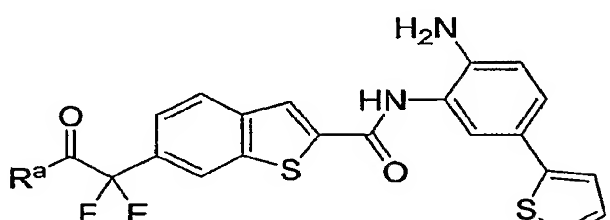
6-(Difluoro-methoxycarbonyl-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester. To a solution of 6-methoxyoxalyl-benzo[b]thiophene-2-carboxylic acid ethyl ester (445 mg, 1.52 mmol) in CH_2Cl_2 (15 mL) at RT was added diethylaminosulfur trifluoride (0.453 mL, 3.43 mmol). After 18 h, LC/MS reveals ~10% starting material, so an additional DAST (0.250 mL) was added. This was repeated every 2h until

the disappearance of the starting material. The reaction mixture was quenched with MeOH (1 mL). The solution was diluted with CH_2Cl_2 (25 mL) and washed with H_2O and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Biotage 25M), eluting with EtOAc/hexane to give a colorless solid. ^{1}H NMR (DMSO-d_6) δ 8.13 (br s, 1H), 8.07 (br s, 1H), 7.94 (br d, J = 8.2 Hz, 1H), 7.61 (br d, J = 8.2 Hz, 1H), 4.42 (q, J = 7.3 Hz, 2H), 3.86 (s, 3H), 1.421 (t, J = 7.3 Hz, 3H). cal'd 315 (MH^+), exp 315 (MH^+).

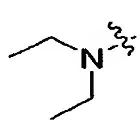
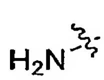


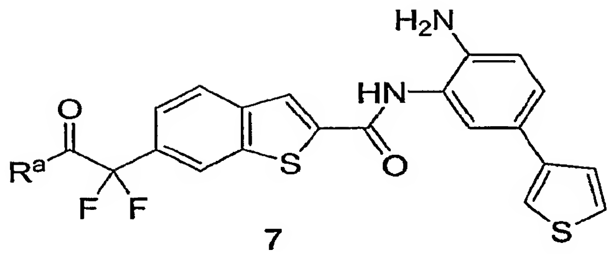
6-(Carboxy-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester. To a solution of 6-(difluoro-methoxycarbonyl-methyl)-benzo[b]thiophene-2-carboxylic acid ethyl ester (200 mg, 0.64 mmol) in MeOH/THF (1/2 mL) was added 1M LiOH (0.67 mL). The resultant solution was stirred overnight and 2N HCl was added dropwise to acidify (~0.7 mL). The solvent was removed *in vacuo* and the solid was used without further purification. cal'd 301 (MH^+), exp 301 (MH^+).

α-aminoaryl analogs were prepared in procedures similar to those described for the preparation of the above 6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide. The compounds were isolated as the free form (parent).

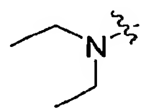


6

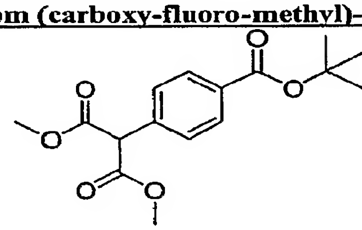
Cpd#	R^a	Name	MS
6-1		6-(Diethylcarbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 500 (MH^+), exp 500 (MH^+)
6-2		6-(Carbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide	cal'd 444 (MH^+), exp 444 (MH^+)



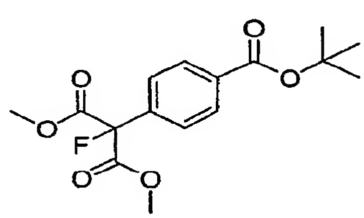
7

Cpd#	R^a	Name	MS
7-1		6-(Diethylcarbamoyl-difluoro-vmethyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide	cal'd 500 (MH^+), exp 500 (MH^+)

Procedures for B1. Compounds from (carboxy-fluoro-methyl)-benzoic acids.

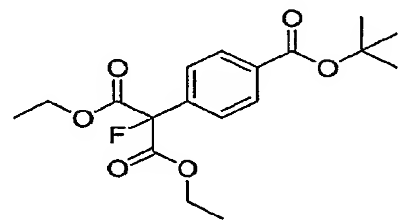


2-(4-tert-Butoxycarbonyl-phenyl)-malonic acid dimethyl ester. To a mixture of *tert*-butyl 4-bromobenzoate (10.1 g, 39.2 mmol), K_3PO_4 (20.2 g, 95.0 mmol), and dimethyl malonate (4.50 mL, 39.2 mmol) was added toluene (69 mL), $Pd_2(dba)_3$ (975 mg, 1.08 mmol), and P(*tert*-Bu)$_3$ (12.8 mL, 10% wt. in hexanes, 4.3 mmol). The reaction mixture was degassed and heated to 85°C. After 2 d, the reaction mixture was diluted with ethyl acetate, washed with water (1 x), brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel (5% to 20% ethyl acetate in hexanes) gave dimethyl [4-(*tert*-butoxycarbonyl)phenyl]malonate as a low melting white solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 4.70 (s, 1H), 3.76 (s, 6H), 1.58 (s, 9H); ESIMS calcd 331.1 (M^+ + Na), found 331.1 (M^+ + Na).

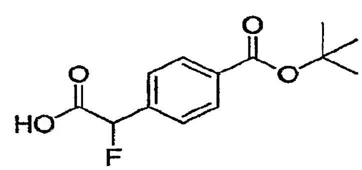


2-(4-tert-Butoxycarbonyl-phenyl)-2-fluoro-malonic acid dimethyl ester. To a solution of dimethyl [4-(*tert*-butoxycarbonyl)phenyl]malonate (1.0 g, 3.24 mmol) in THF (10 mL) at 0°C was added sodium hydride (0.14 g, 3.6 mmol, 60% dispersion in mineral oil). The reaction was stirred at 0°C for 15 minutes. A solution of Selectfluor (1.26 g, 3.6 mmol) in DMF (10 mL) was added and the reaction was allowed to warm to ambient temperature and stir under nitrogen for 1 hour. The reaction was quenched with ammonium chloride solution and partitioned between water/ethyl acetate. The organics were dried

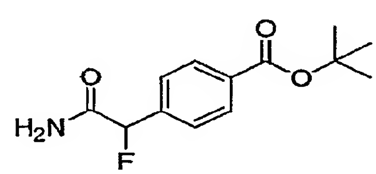
over sodium sulfite, filtered and evaporate. Purification by flash chromatography (0-20% ethyl acetate/hexanes) gave the desired product as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 3.86 (s, 3H), 1.58 (s, 9H); ESIMS calcd 349.1 (M^+ + Na), found 349.1 (M^+ + Na).



2-(4-tert-Butoxycarbonyl-phenyl)-2-fluoro-malonic acid diethyl ester. A stirred slurry of α-fluoro-diethyl malonate (6.93 g, 38.9 mmol), 4-bromo-benzoic acid tert-butyl ester (10 g, 38.9 mmol) and potassium phosphate (21.5 g, 101 mmol) was degassed, then bis(tri-t-butylphosphine)palladium(0) (0.994 g, 1.95 mmol) was added. The resulting mixture was degassed again before stirring at 85°C under N_2 over the weekend. The mixture was cooled, diluted with EtOAc (100 mL), washed with water, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. Purification of the residue by MPLC using 2-20% EtOAc/Hexanes gave 2-(4-tert-butoxycarbonyl-phenyl)-2-fluoro-malonic acid diethyl ester. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.2 Hz, 2H), 4.31 (q, J = 7.5 Hz, 4H), 1.29 (t, J = 7.5 Hz, 6H); cal'd 355 (MH^+), exp 355 (MH^+).

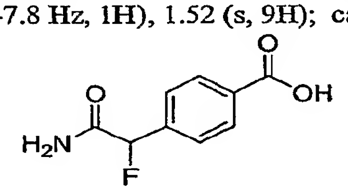


4-(Carboxy-fluoro-methyl)-benzoic acid tert-butyl ester. A stirred solution of 2-(4-tert-butoxycarbonyl-phenyl)-2-fluoro-malonic acid diethyl ester (2.97 g, 8.38 mmol) in MeOH/THF (5/15 mL) was added 2M NaOH (12.6 mL) and then the mixture was degassed. After 18 h, the solution was heated to 60°C for 30 min. The mixture was cooled, diluted with EtOAc (100 mL), washed with water, and 0.5 N citric acid, then dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. To the residue was added EtOAc and H_2O, and the mixture was heated to 100°C for 1h. The mixture was cooled, diluted with EtOAc (100 mL), washed with water, and 0.5 N citric acid, then dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The material was used w/o further purification. cal'd 255 (MH^+), exp 255 (MH^+).



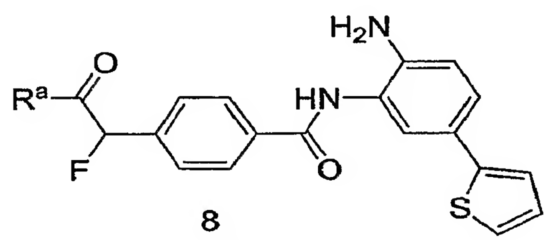
4-(Fluoro-methylcarbamoyl-methyl)-benzoic acid tert-butyl ester. To a solution of 4-(carboxy-fluoro-methyl)-benzoic acid tert-butyl ester (800 mg, 3.15 mmol), NMM (1.2 eq), and oxalyl chloride (0.33 mL,

3.78 mmol) in CH_2Cl_2 (20 mL) was added one drop of DMF. The solution was stirred for 1 h, then added to a solution of ammonium hydroxide (1.9 mL, 15.7 mmol) in CH_2Cl_2 (10 mL). After 30 min, the solvent was removed. The residue was diluted with CH_2Cl_2 (50 mL), washed with water, then dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The material was used w/o further purification. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.91 (d, J = 8.2 Hz, 2H), 7.89 (br s, 1H), 7.59 (br s, 1H), 7.53 (d, J = 8.2 Hz, 2H), 5.87 (d, J = 47.8 Hz, 1H), 1.52 (s, 9H); cal'd 254 (MH^+), exp 254 (MH^+).

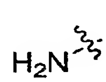
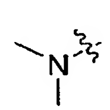


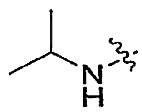
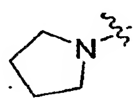
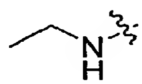
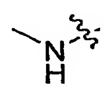
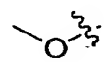
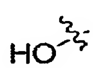
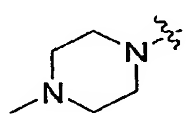
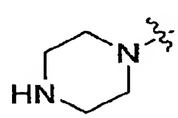
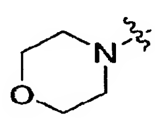
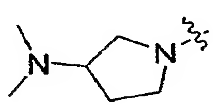
4-(Carbamoyl-fluoro-methyl)-benzoic acid. To a solution 4-(fluoro-methylcarbamoyl-methyl)-benzoic acid tert-butyl ester (309 mg, 1.22 mmol)) in methylene chloride (2 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at ambient temperature for 4 hours. The reaction was evaporated to dryness. The material was used w/o further purification. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.17 (s, 1H), 7.96 (d, J = 8.2 Hz, 2H), 7.85 (br s, 1H), 7.60 (br s, 1H), 7.53 (d, J = 8.2 Hz, 2H), 5.88 (d, J = 47.8 Hz, 1H); cal'd 198 (MH^+), exp 198 (MH^+).

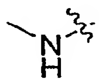
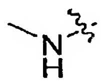
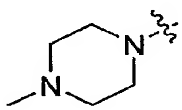
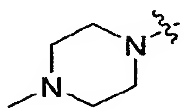
α-aminoaryl analogs were prepared in procedures similar to those described for the preparation of the above 6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide. Optically pure compounds were prepared via separation of Boc-protected intermediates using chiral chromatography and subsequent individual deprotection. All compounds were prepared as the free base (parent) form.

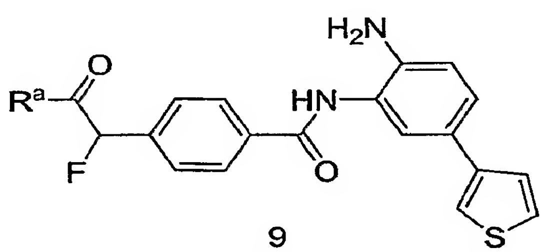


8

Cpd#	R^a	Name	MS
8-1		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-fluoro-methyl)-benzamide	cal'd 370 (MH^+), exp 370 (MH^+)
8-2		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(dimethylcarbamoyl-fluoro-methyl)-benzamide	cal'd 398 (MH^+), exp 398 (MH^+)

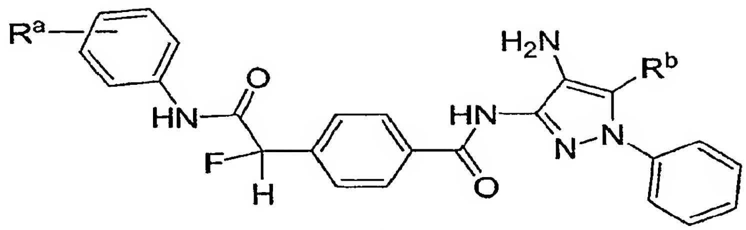
8-3		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(fluoro-isopropylcarbamoyl-methyl)-benzamide	cal'd 412 (MH^+), exp 412 (MH^+)
8-4		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-oxo-2-pyrrolidin-1-yl-ethyl)-benzamide	cal'd 424 (MH^+), exp 424 (MH^+)
8-5		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(ethylcarbamoyl-fluoro-methyl)-benzamide	cal'd 398 (MH^+), exp 398 (MH^+)
8-6		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(fluoro-methylcarbamoyl-methyl)-benzamide	cal'd 384 (MH^+), exp 384 (MH^+)
8-7		[4-(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-phenyl]-fluoro-acetic acid methyl ester	cal'd 385 (MH^+), exp 385 (MH^+)
8-8		[4-(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-phenyl]-fluoro-acetic acid	cal'd 371 (MH^+), exp 371 (MH^+)
8-9		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[1-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide	cal'd 453 (MH^+), exp 453 (MH^+)
8-10		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-oxo-2-piperazin-1-yl-ethyl)-benzamide	cal'd 439 (MH^+), exp 439 (MH^+)
8-11		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-morpholin-4-yl-2-oxo-ethyl)-benzamide	cal'd 440 (MH^+), exp 440 (MH^+)
8-12		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[2-(3-dimethylamino-pyrrolidin-1-yl)-1-fluoro-2-oxo-ethyl]-	cal'd 467 (MH^+), exp 467 (MH^+)

		benzamide	
8-13		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-((*S*)-fluoro-methylcarbamoyl-methyl)-benzamide	cal'd 384 (MH^+), exp 384 (MH^+)
8-14		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-((*R*)-fluoro-methylcarbamoyl-methyl)-benzamide	cal'd 384 (MH^+), exp 384 (MH^+)
8-15		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[(1*R*)-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide	cal'd 453 (MH^+), exp 453 (MH^+)
8-16		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[(1*S*)-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide	cal'd 453 (MH^+), exp 453 (MH^+)
8-17	H_2N	N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-(*S*)-fluoro-methyl)-benzamide	cal'd 370 (MH^+), exp 370 (MH^+)
8-18	H_2N	N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-(*R*)-fluoro-methyl)-benzamide	cal'd 370 (MH^+), exp 370 (MH^+)



9

Cpd#	R^a	Name	MS
9-1	H_2N	N-(2-Amino-5-thiophen-3-yl-phenyl)-4-(carbamoyl-fluoro-methyl)-benzamide	cal'd 370 (MH^+), exp 370 (MH^+)

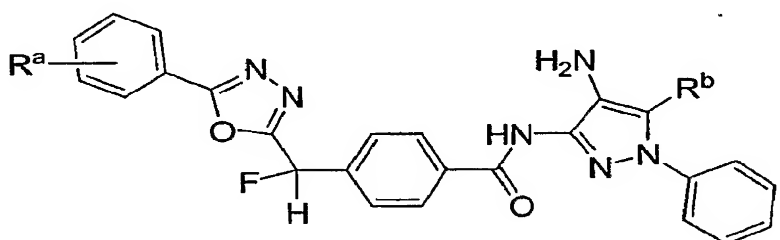


10

Cpd#	R^a	R^b	Name	MS
10-1	3-CN	H	N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-[(3-cyano-phenylcarbamoyl)-fluoro-methyl]-benzamide	cal'd 455.1 (MH^+), exp 455.0 (MH^+)

Oxadiazoles

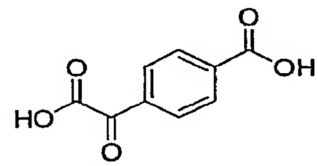
α-aminoaryl analogs were prepared in procedures similar to those described for the preparation of analogs from 6-[fluoro(5-phenyl-1,3,4-oxadiazol-2-yl)methyl]-1-benzothiophene-2-carboxylic acid. Unless otherwise indicated, the compounds were prepared as the free base (parent) form.



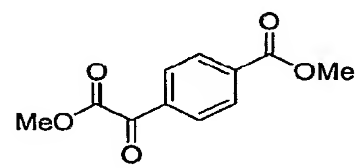
11

Cpd#	R^a	R^b	Name	MS
11-1	2-OMe	H	N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide; isolated as the TFA salt	cal'd 485.1 (MH^+), exp 485.1 (MH^+)
11-2	2-OMe	F	N-(4-Amino-5-fluoro-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide	cal'd 503.1 (MH^+), exp 503.1 (MH^+)

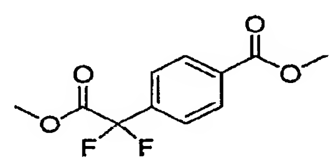
Procedures for B2. Compounds from (carboxy-difluoro-methyl)-benzoic acids.



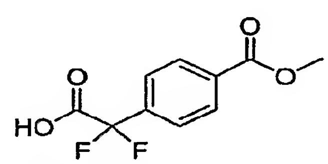
4-Oxalyl-benzoic acid. To a solution of ethyl (4-cyanophenyl)(oxo)acetate (5.0 g, 24.6 mmol) in water (100 mL) was added concentrated hydrochloric acid (100 mL). The solution was heated to reflux for 16 hours. The solution was cooled to ambient temperature and the solids were filtered and dried to give 4-(carboxycarbonyl)benzoic acid as a white solid. ESIMS calcd 195.0 (M^+ + H), found 195.0 (M^+ + H).



4-Methoxyoxalyl-benzoic acid methyl ester. To a solution of 4-(carboxycarbonyl)benzoic acid (4.55 g, 23.4 mmol) in methanol (100 mL) was added thionyl chloride (7.0 g, 58.6 mmol) dropwise. The reaction was stirred at ambient temperature for 16 hours then evaporated to dryness to give methyl 4-[methoxy(oxo)acetyl]benzoate as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.15 (m, 2H), 8.09 (m, 2H), 3.99 (s, 3H), 3.96 (s, 3H); ESIMS calcd 223.0 (M^+ + H), found 223.0 (M^+ + H).



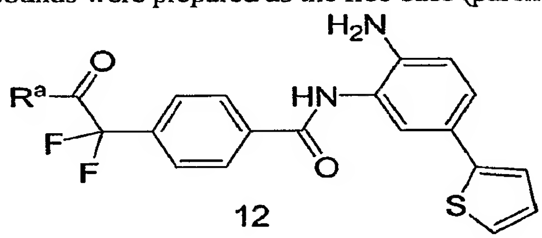
4-(Difluoro-methoxycarbonyl-methyl)-benzoic acid methyl ester. To a solution of methyl 4-[methoxy(oxo)acetyl]benzoate (4.88 g, 22.0 mmol) in methylene chloride (300 mL) was added [bis(2-methoxyethyl)amino]sulfur trifluoride (10.2 g, 46.1 mmol) and the resulting solution was stirred for 16 hours at ambient temperature. The reaction was evaporated to dryness and purified by flash chromatography (0-10% ethyl acetate/hexanes) to give methyl 4-(1,1-difluoro-2-methoxy-2-oxoethyl)benzoate as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.11 (d, J = 8.51 Hz, 2H), 7.67 (d, J = 8.51 Hz, 2H), 3.93 (s, 3H), 3.85 (s, 3H); ESIMS calcd 245.1 (M^+ + H), found 245.0 (M^+ + H).



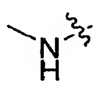
4-(Carboxy-difluoro-methyl)-benzoic acid methyl ester. To a solution of methyl 4-(1,1-difluoro-2-methoxy-2-oxoethyl)benzoate (1.0 g, 4.1 mmol) in THF (20 mL) was added sodium hydroxide (4.1 mmol, 4.1 mL of a 1M solution) dropwise at ambient temperature. The resulting solution was stirred for

16 hours. The reaction was partitioned between 1M HCl and ethyl acetate. The organics were dried over sodium sulfate, filtered and evaporated to give difluoro[4-(methoxycarbonyl)phenyl]acetic acid as a white solid. [1]H NMR ($CDCl_3$) δ 8.12 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.21 Hz, 2H), 3.94 (s, 3H), 3.0 (bs, 1H); ESIMS calcd 231.0 (M^+ + H), found 231.0 (M^+ + H).

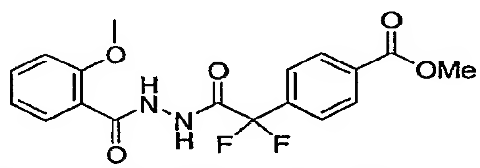
α-aminoaryl analogs were prepared in procedures similar to those described for the preparation of the above 6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide. All compounds were prepared as the free base (parent) form.



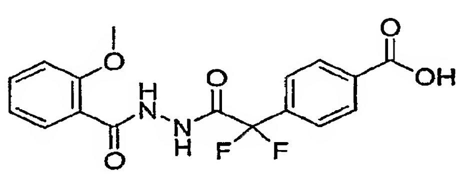
12

Cpd#	R^a	Name	MS
12-1		N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(difluoro-methylcarbamoyl-methyl)-benzamide	cal'd 402 (MH^+), exp 402 (MH^+)

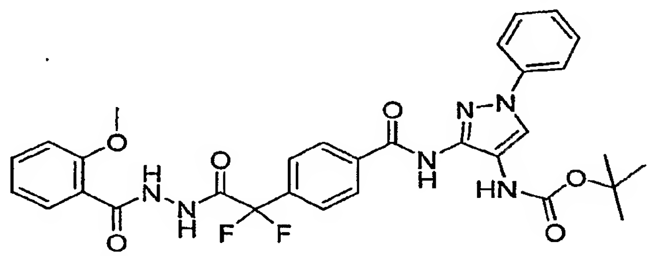
<u>**Oxadiazoles**</u>



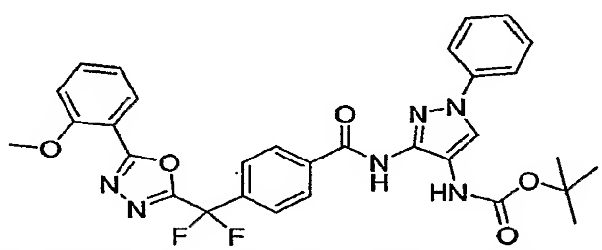
4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoate. To a solution of difluoro[4-(methoxycarbonyl)phenyl]acetic acid (0.12g, 0.52 mmol) and 2-methoxybenzohydrazide (0.13 g, 0.78 mmol) in methylene chloride (2 mL) was added 3-{[(ethylimino)methylene]amino}-*N,N*-dimethylpropan-1-aminium chloride (0.2 g, 1.04 mmol). The resulting solution was stirred at ambient temperature for 16 hours. The reaction was purified by flash chromatography (0-4% methanol/methylene chloride) to give methyl 4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoate as a white solid. ESIMS calcd 379.1 (M^+ + H), found 379.1 (M^+ + H).



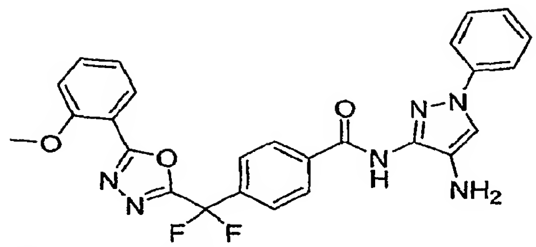
4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoic acid. To a solution of methyl 4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoate (74 mg, 0.2 mmol) in THF (3 mL) was added sodium hydroxide (0.58 mmol, 0.58 mL of a 1M solution) and the solution was stirred at ambient temperature for 16 hours. The reaction was partitioned between 1M HCl and ethyl acetate. The organics were dried over sodium sulfate, filtered and evaporated to give 4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoic acid as a white solid. ESIMS calcd 365.0 (M^+ + H), found 365.0 (M^+ + H).



***tert*-butyl {3-[(4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate.** To a solution of 4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoic acid (65 mg, 0.18 mmol), *tert*-butyl (3-amino-1-phenyl-1*H*-pyrazol-4-yl)carbamate (74 mg, 0.27 mmol) and N,N-diisopropylethylamine (46mg, 0.36 mmol) in methylene chloride (1.5 mL) was added (1*H*-1,2,3-benzotriazol-1-yloxy)(triisopropyl)phosphonium hexafluorophosphate (0.16 g, 0.36 mmol) and the reaction was sealed and heated to 60°C for 16 hours. The reaction was purified by flash chromatography (0-4% methanol/methylene chloride) to give crude *tert*-butyl {3-[(4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate. ESIMS calcd 621.2 (M^+ + H), found 621.2 (M^+ + H).

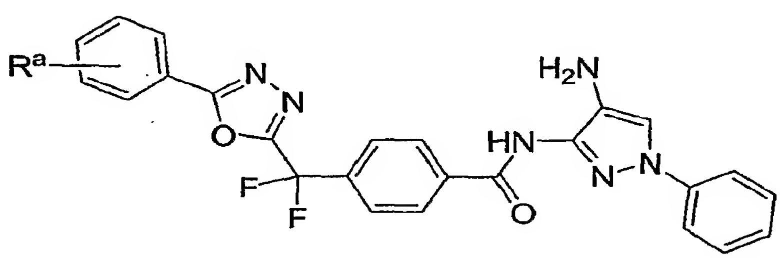


***tert*-butyl {3-[(4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzoyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate.** To a solution of *tert*-butyl {3-[(4-{1,1-difluoro-2-[2-(2-methoxybenzoyl)hydrazino]-2-oxoethyl}benzoyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate (0.05 g, 0.08 mmol) in THF (2 mL) was added Burgess reagent (38 mg, 0.16 mmol) and the reaction was sealed and heated to 100°C for 10 minutes under microwave irradiation. The reaction was evaporated to dryness and purified by reverse phase chromatography (5/95 acetonitrile/water to 95/5 acetonitrile/water) to give *tert*-butyl {3-[(4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzoyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate as a white solid. ESIMS calcd 603.2 (M^+ + H), found 603.2 (M^+ + H).



N-(4-amino-1-phenyl-1H-pyrazol-3-yl)-4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzamide. To a solution of *tert*-butyl {3-[(4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzoyl)amino]-1-phenyl-1*H*-pyrazol-4-yl}carbamate (10 mg) in methylene chloride (2 mL) was added trifluoroacetic acid (1 mL) and the solution was stirred at ambient temperature for 16 hours. The reaction was evaporated to dryness to give *N*-(4-amino-1-phenyl-1*H*-pyrazol-3-yl)-4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzamide as a yellowish solid. ^{1}H NMR (CD_3OD) δ 8.45 (s, 1H), 8.23 (d, J = 8.21 Hz, 2H), 7.93 (m, 3H), 7.79 (d, J = 7.62 Hz, 2H), 7.64 (m, 1H), 7.52 (t, J = 7.62 Hz, 2H), 7.37 (t, J = 7.62 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.14 (t, J = 7.62 Hz, 1H), 3.96 (s, 3H); ESIMS calcd 503.2 (M^+ + H), found 503.1 (M^+ + H).

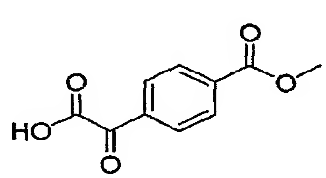
α-aminoaryl analogs from the carboxylic acids were prepared in procedures similar to those described for the preparations of the above examples. All compounds were prepared as the TFA salt form.



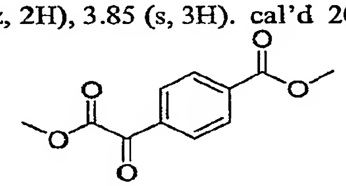
13

Cpd#	R^a	Name	MS
13-1	2-OMe	N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{difluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide	cal'd 503.1 (MH^+), exp 503.1 (MH^+)

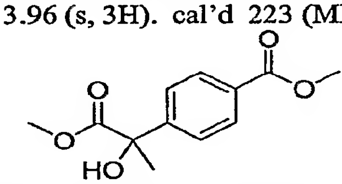
<u>**Procedure for B3. Compounds from (fluoro-alkoxycarbonyl-alkyl)-benzoic acids.**</u>



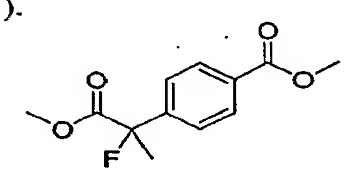
4-Carboxyoxalyl-benzoic acid methyl ester. To solution of 4-acetyl-benzoic acid methyl ester (15 g, 84.0 mmol) in pyridine (40 mL) at 90°C was added selenium dioxide (16.4 g, 147 mmol) portionwise over 2h. After 18 h, cooled to RT and filtered via Celite. The solvent was removed *in vacuo* and the residue was diluted with EtOAc, washed with 0.5N HCl, dried (MgSO4) and the solvent was evaporated under reduced pressure. The material was used without further purification. ^{1}H NMR (DMSO-d_6) δ 8.01 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H), 3.85 (s, 3H). cal'd 209 (MH^+), exp 209 (MH^+).



4-Methoxyoxalyl-benzoic acid methyl ester. To a solution 4-carboxyoxalyl-benzoic acid methyl ester (5.0 g, 24.0 mmol) and triethylamine (3.35 mL, 24.0 mmol) in CH_2Cl_2 (50 ml) at RT was added methyl chloroformate (1.86 mL, 24.0 mmol). After 30 min, the reaction mixture was diluted with CH_2Cl_2 (100 ml) and washed with H_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (Biotage 25M), eluting with EtOAc/hexane to give a colorless solid. ^{1}H NMR ($CDCl_3$) δ 8.16 (d, J = 8.2 Hz, 2H), 8.09 (d, J = 8.2 Hz, 2H), 3.99 (s, 3H), 3.96 (s, 3H). cal'd 223 (MH^+), exp 223 (MH^+).

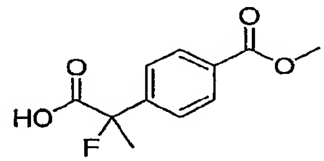


4-(1-Hydroxy-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester. To a slurry of 4-methoxyoxalyl-benzoic acid methyl ester (0.913 g, 4.11 mmol) in THF (20 ml) at -78 °C was added methyl magnesium chloride (2.74 mL, 8.22 mmol). During the addition the slurry became homogeneous. Let warm to RT overnight. The reaction was diluted with EtOAc and H_2O. The combined organic fractions were dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel Biotage 25M, eluting with EtOAc/hexane to give as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.2 Hz, 2H), 3.90 (s, 3H), 3.78 (s, 3H), 1.78 (s, 3H). cal'd 239 (MH^+), exp 239 (MH^+).

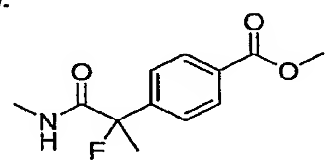


4-(1-Fluoro-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester. To a solution of 4-(1-hydroxy-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester (365 mg, 1.53 mmol) in CH_2Cl_2 (5 ml) at 0 °C was added DAST (0.25 ml, 1.89 mmol). After 1.5h, let warm to RT. The reaction was quenched with MeOH, diluted with CH_2Cl_2, washed with H_2O. The organic layer was dried ($MgSO_4$) filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel Biotage 25M, eluting with EtOAc/hexane to give as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.04 (d, J =

8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 3.92 (s, 3H), 3.76 (s, 3H), 1.94 (d, J = 22.3 Hz, 3H). cal'd 241 (MH^+), exp 241 (MH^+).

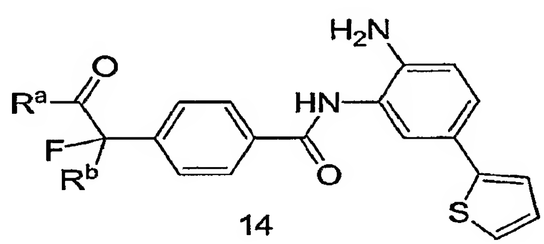


4-(1-Carboxy-1-fluoro-ethyl)-benzoic acid methyl ester. To a solution of 4-(1-fluoro-1-methoxycarbonyl-ethyl)-benzoic acid methyl ester (288 mg, 1.20 mmol) in THF/MeOH (2/2 mL) was added lithium hydroxide (1.26 mmol, 1.26 mL of a 1M solution) dropwise at ambient temperature. The resulting solution was stirred for 3 hours. The reaction was diluted with H_2O and washed with EtOAc. The aqueous fractions were acidified with 1 N HCl and extracted with EtOAc. The organics were dried over sodium sulfate, filtered and evaporated to a white solid, which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 3.92 (s, 3H), 1.98 (d, J = 22.3 Hz, 3H). cal'd 227 (MH^+), exp 227 (MH^+).



4-(1-Fluoro-1-methylcarbamoyl-ethyl)-benzoic acid methyl ester. To a solution of 4-(1-carboxy-1-fluoro-ethyl)-benzoic acid methyl ester (200 mg, 0.884 mmol), HOBT (179 mg, 1.326 mmol), methylamine hydrochloride (179 mg, 2.65 mmol) and Et_3N (0.431 mL, 3.09 mmol) in CH_2Cl_2 (5 mL) was added EDC (254 mg, 1.326 mmol). The mixture was stirred overnight. The solvent was removed. The residue was dissolved in EtOAc and washed with H_2O, 0.5 N HCl, sat. $NaHCO_3$, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was used without further purification. ^{1}H NMR ($CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), 6.48 (br s, 1H), 3.90 (s, 3H), 2.83 (d, J = 5.3 Hz, 3H), 1.98 (d, J = 23.5 Hz, 3H). cal'd 240 (MH^+), exp 240 (MH^+).

α-aminoaryl analogs were prepared in procedures similar to those described for the preparation of the above 6-[(4-chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide. All compounds were prepared as the free base (parent) form.



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Cpd#	R^a	R^b	Name	MS
14-1	NHMe	Me	N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-1-methylcarbamoyl-ethyl)-benzamide	cal'd 398 (MH^+), exp 398 (MH^+)

EXAMPLE 2 – HDAC INHIBITION BY NOVEL COMPOUNDS

HDAC1-Flag Assay:

Novel compounds were tested for their ability to inhibit histone deacetylase, subtype 1 (HDAC1) using an in vitro deacetylation assay. The enzyme source for this assay was an epitope-tagged human HDAC1 complex immuno-purified from stably expressing mammalian cells. The substrate consisted of a commercial product containing an acetylated lysine side chain (BIOMOL Research Laboratories, Inc., Plymouth Meeting, PA). Upon deacetylation of the substrate by incubation with the purified HDAC1 complex, a fluorophore is produced that is directly proportional to the level of deacetylation. Using a substrate concentration at the Km for the enzyme preparation, the deacetylation assay was performed in the presence of increasing concentrations of novel compounds to semi-quantitatively determine the concentration of compound required for 50% inhibition (IC50) of the deacetylation reaction.

EXAMPLE 3 – HDAC INHIBITION IN CELL LINES

ATP Assay

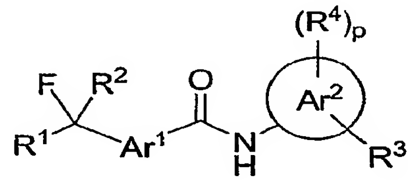
The novel compounds of the present invention were tested for their ability to inhibit proliferation of the human cervical cancer (HeLa) and colon carcinoma (HCT116) cells.

In this assay, also referred to as the Vialight Assay, cellular ATP levels are measured as a means of quantifying cellular proliferation. This assay makes use of a bioluminescent method from Cambrex (ViaLight PLUS, cat. #LT07-121). In the presence of ATP, luciferase converts luciferin to oxyluciferin and light. The amount of light produced (emission at 565nM) is measured and correlates with a relative amount of proliferation. Human cervical cancer (HeLa) or colon carcinoma (HCT116) cells were incubated with vehicle or increasing concentrations of compound for 48 hours. Cell proliferation was quantified by adding the cell lysis reagent (provided in the Vialight assay kit) directly to culture wells, followed by addition of the ATP-monitoring reagent (containing luciferase/luciferin). The amount of light produced is then measured (emission at 565nM). The quantity of light produced, as measured by 565nM absorbance, is directly proportional to the number of living cells in culture.

While this invention has been particularly shown and described with references to embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the meaning of the invention described. Rather, the scope of the invention is defined by the claims that follow.

WHAT IS CLAIMED IS:

1. A compound represented by the Formula I:



I

wherein:

Ar^1 is selected from: heteroaryl and aryl, wherein the aryl and heteroary l is optionally substituted with from 1 to 2 of R^6;

Ar^2 is a 5 to 6 membered heteroaryl or aryl;

R^1 is selected from: $R^5C(O)$-, aryl, heteroaryl and heterocyclic, wherein the aryl, heteroaryl and heterocyclic is optionally substituted with from 1 to 3 of the substituent R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9; or

R^1 and R^2 are combined to form -$(CHR^9)_u$- wherein one or more of the carbon atoms may be optionally replaced by a moiety selected from O, $S(O)_m$, -$N(R^{10})C(O)$-, and -NR^{11}-;

R^3 is OH, SH or NH_2;

R^4 is independently selected from hydrogen, OH, NH_2, nitro, CN, amide, carboxyl, C_1-C_7 alkoxy, C_1-C_7 alkyl, C_1-C_7 haloalkyl, C_1-C_7 haloalkyloxy, C_1-C_7 hydroxyalkyl, C_1-C_7 alkenyl, C_1-C_7 alkyl-C(=O)O-, C_1-C_7 alkyl-C(=O)-, C_1-C_7 alkynyl, halo group, amide, hydroxyalkoxy, -$NHSO_2$, -SO_2NH, C_1-C_7 alkyl-$NHSO_2$-, C_1-C_7 alkyl-SO_2NH-, C_1-C_7 alkylsulfonyl, C_1-C_7 alkylamino, di(C_1-C_7)alkylamino and L_2-R^8, wherein R^8 is heteroaryl, heterocyclic, aryl, or C_3-C_8 cycloalkyl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, C_1-C_4 alkylene, C_1-C_4 alkynyl, C_1-C_4 alkenyl, -O-, -S-, -N-, -C(=O)NH-, -NHC(=O)-, -NHC(=O)NH-, -SO_2NH-, -$NHSO_2$-, -SO_2-, -C(=O)- or -C(=O)O- ;

R^5 is selected from: amino, C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl,

heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, aryl, heteroaryl and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino, N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), and sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

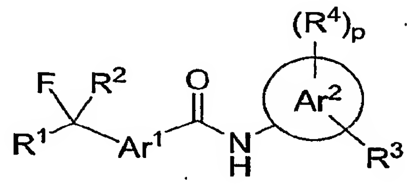
R^{10} is selected from: hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, heterocyclic, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^{11} is selected from: hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, heterocyclic and -C(O)-R (where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl),wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

p is 1, 2, 3 or 4;
u is 3, 4 or 5;

or a stereoisomer or pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1 of the Formula I:



I

wherein:

Ar^1 is selected from: heteroaryl and aryl, wherein the aryl and heteroary l is optionally substituted with from 1 to 2 of R^6;
Ar^2 is a 5 to 6 membered heteroaryl or aryl;

R^1 is selected from: $R^5C(O)$- and [1,3,4]oxadiazol-2-yl, wherein the [1,3,4]oxadiazol-2-yl is optionally substituted with R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is OH, SH or NH_2;
R^4 is independently selected from hydrogen, OH, NH_2, nitro, CN, amide, carboxyl, C_1-C_7 alkoxy, C_1-C_7 alkyl, C_1-C_7 haloalkyl, C_1-C_7 haloalkyloxy, C_1-C_7 hydroxyalkyl, C_1-C_7 alkenyl, C_1-C_7 alkyl-C(=O)O-, C_1-C_7 alkyl-C(=O)-, C_1-C_7 alkynyl, halo group, amide, hydroxyalkoxy, $-NHSO_2$, $-SO_2NH$, C_1-C_7 alkyl-$NHSO_2$-, C_1-C_7 alkyl-SO_2NH-, C_1-C_7 alkylsulfonyl, C_1-C_7 alkylamino or di(C_1-C_7)alkylamino or L_2-R^8, wherein R^8 is heteroaryl, heterocyclic, aryl, or C_3-C_8 cycloalkyl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, C_1-C_4 alkylene, C_1-C_4 alkynyl, C_1-C_4 alkenyl, -O-, -S-, -N-, -C(=O)NH-, -NHC(=O)-, -NHC(=O)NH-, $-SO_2NH$-, $-NHSO_2$-, $-SO_2$-, -C(=O)- or -C(=O)O- ;

R^5 is selected from: amino, C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10}

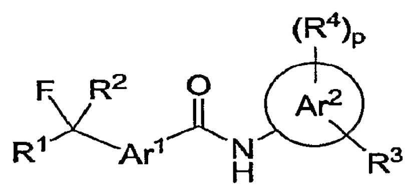
dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, aryl, heteroaryl and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), C_1-C_{10} haloalkyl, hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

p is 1, 2, 3 or 4;
or a stereoisomer or pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1 of the Formula I:



I

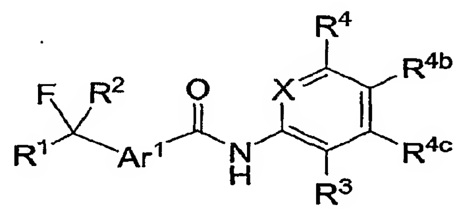
wherein:

Ar^2 is selected from phenyl, pyridyl, thienyl, pyrazolyl and pyrrolyl;

R^2 is selected from hydrogen, C_1-C_6 alkyl, fluoro and aryl, wherein the alkyl and aryl are optionally substituted with from 1 to 3 of the substituent R^9;
R^3 is NH_2;
and the remaining substituents and variables are as described in Claim 1;

or a stereoisomer or pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the Formula II:



II

wherein:

Ar^1 is selected from: heteroaryl and aryl;

X is CR^{4a} or N;

R^1 is selected from: $R^5C(O)$- and [1,3,4]oxadiazol-2-yl, wherein the [1,3,4]oxadiazol-2-yl is optionally substituted with R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is OH, SH or NH_2;

R^4 is selected from hydrogen, C_1-C_7 alkyl and L_2-R^8, wherein R^8 is heteroaryl or aryl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, and C_1-C_4 alkylene;

R^{4a}, R^{4b} and R^{4c}, are independently selected from hydrogen and fluoro;

R^5 is selected from: C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-

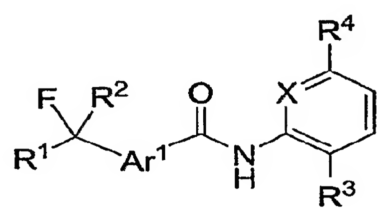
arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8 cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

or a stereoisomer or pharmaceutically acceptable salt thereof.

5. The compound according to Claim 4 of the Formula III:



III

wherein:

X is CH;

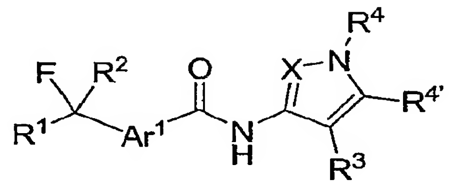
R^2 is selected from hydrogen, C_1-C_6 alkyl, fluoro and aryl, wherein the alkyl and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is NH_2;

and the remaining substituents and variables are as described above for the compounds of Formula II in Claim 4;

or a stereoisomer or pharmaceutically acceptable salt thereof.

6. The compound according to Claim 1 of the Formula IV:



IV

wherein:

Ar^1 is selected from: heteroaryl and aryl;

X is CH or N;

R^1 is selected from: $R^5C(O)$- and [1,3,4]oxadiazol-2-yl, wherein the [1,3,4]oxadiazol-2-yl is optionally substituted with R^6;

R^2 is selected from hydrogen, C_1-C_6 alkyl, halo, C_3-C_8 cycloalkyl, heteroaryl, heterocyclic and aryl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic and aryl are optionally substituted with from 1 to 3 of the substituent R^9;

R^3 is OH, SH or NH_2;

R^4 is selected from hydrogen, C_1-C_7 alkyl and L_2-R^8, wherein R^8 is heteroaryl or aryl, which R^8 is optionally substituted with from 1 to 3 of the substituent R^6, L_2 is selected from a bond, and C_1-C_4 alkylene;

$R^{4'}$ is selected from hydrogen and fluoro;

R^5 is selected from: C_1-C_{10} alkylamino; C_3-C_8 cycloalkylamino; arylamino, heterocyclylamino, heteroarylamino, C_1-C_{10} aralkylamino, C_1-C_{10} heteroaralkylamino, OH, C_1-C_{10} alkoxy, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic, aryl, piperidin-1-yl, pyrrolidin-1-yl, piperazin-1-yl, and morpholin-4-yl are optionally substituted with from 1 to 3 of the substituent R^6;

R^6 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino or N,N-C_1-C_{10} dialkylamino, N-arylamino or N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), sulfonamide (-$NHS(O)_2R$, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), C_3-C_8

cycloalkyl, C_1-C_{10} alkylaryl, C_1-C_{10} alkylheterocyclyl, C_1-C_{10} alkylcycloalkyl, and aryloxy, wherein the alkyl, cycloalkyl, heteroaryl, heterocyclic or aryl is optionally substituted with from 1 to 3 of the substituent R^7;

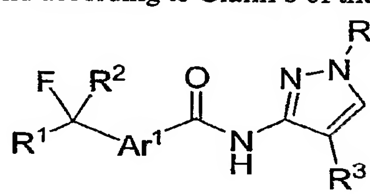
R^7 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino, N,N-C_1-C_{10} dialkylamino, N-arylamino, N,N-diarylamino, ester (-C(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), urea (-NHC(O)-NHR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), carbamate (-NHC(O)-OR, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl), and sulfonamide (-NHS(O)$_2$R, where R is a group selected from C_1-C_{10} alkyl, aryl and heteroaryl);

R^9 is selected from: C_1-C_{10} alkyl, C_1-C_{10} alkoxy, a halogen or halo group (F, Cl, Br, I), hydroxy, nitro, oxo, -CN, -COH, -COOH, amino, azido, N-C_1-C_{10} alkylamino and N,N-C_1-C_{10} dialkylamino;

$R^{4'}$ is selected from hydrogen and fluoro;

or a stereoisomer or pharmaceutically acceptable salt thereof.

7. The compound according to Claim 6 of the Formula V:



V

wherein:
R^2 is selected from hydrogen, C_1-C_6 alkyl, fluoro and aryl, wherein the alkyl and aryl are optionally substituted with from 1 to 3 of the substituent R^9;
R^3 is NH_2;
and the remaining substituents and variables are as described above in Claim 6;

or a stereoisomer or pharmaceutically acceptable salt thereof.

8. A compound selected from:

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Fluoro-phenylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(4-Chloro-phenylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(4-Chloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-{[1-(*S*)-(4-Chloro-phenyl)-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(2,4-Dichloro-benzylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Fluoro-methylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(4-Amino-biphenyl-3-ylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[(2,2-Difluoro-1-phenyl-ethylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-{[1-(*R*)-(4-Chloro-phenyl)-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-[Fluoro-(indan-1-(*S*)-ylcarbamoyl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-{[1-(*S*)-Phenyl-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Fluoro-methylcarbamoyl-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-[Fluoro-(1-(*S*)-phenyl-ethylcarbamoyl)-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-[(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-fluoro-methyl]-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide;

6-(Carbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-{Fluoro-[(pyridin-3-ylmethyl)-carbamoyl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

N-(4-amino-1-phenyl-1H-pyrazol-3-yl)-6-[2-(benzylamino)-1-fluoro-2-oxoethyl]-1-benzothiophene-2-carboxamide;

6-[Fluoro-(5-methyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-{Fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-[Fluoro-(5-phenyl-[1,3,4]oxadiazol-2-yl)-methyl]-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide;

6-(Diethylcarbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Carbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-2-yl-phenyl)amide;

6-(Diethylcarbamoyl-difluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-fluoro-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(dimethylcarbamoyl-fluoro-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(fluoro-isopropylcarbamoyl-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-oxo-2-pyrrolidin-1-yl-ethyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(ethylcarbamoyl-fluoro-methyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(fluoro-methylcarbamoyl-methyl)-benzamide;

[4-(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-phenyl]-fluoro-acetic acid methyl ester;

[4-(2-Amino-5-thiophen-2-yl-phenylcarbamoyl)-phenyl]-fluoro-acetic acid;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[1-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-oxo-2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-2-morpholin-4-yl-2-oxo-ethyl)-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[2-(3-dimethylamino-pyrrolidin-1-yl)-1-fluoro-2-oxo-ethyl]-benzamide;

N-(2-Amino-5-thiophen-3-yl-phenyl)-4-(carbamoyl-fluoro-methyl)-benzamide;

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-[(3-cyano-phenylcarbamoyl)-fluoro-methyl]-benzamide;

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide;

N-(4-Amino-5-fluoro-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(difluoro-methylcarbamoyl-methyl)-benzamide;

N-(4-amino-1-phenyl-1*H*-pyrazol-3-yl)-4-{difluoro[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}benzamide;

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{difluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide;

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(1-fluoro-1-methylcarbamoyl-ethyl)-benzamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

9. A compound selected from:

6-{[1-(*S*)-Phenyl-ethylcarbamoyl]-fluoro-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-biphenyl-3-yl)amide; TFA salt;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid (2-amino-5-thiophen-3-yl-phenyl)amide; TFA salt;

6-(Benzylcarbamoyl-fluoro-methyl)-benzo[b]thiophene-2-carboxylic acid [4-amino-1-(3-chloro-phenyl)-1H-pyrazol-3-yl]-amide; TFA salt;

6-{Fluoro-[(pyridin-3-ylmethyl)-carbamoyl]-methyl}-benzo[b]thiophene-2-carboxylic acid (4-amino-1-phenyl-1H-pyrazol-3-yl)amide; HCl salt; or

N-(4-Amino-1-phenyl-1H-pyrazol-3-yl)-4-{fluoro-[5-(2-methoxy-phenyl)-[1,3,4]oxadiazol-2-yl]-methyl}-benzamide; TFA salt.

10. The compound according to Claim 1 selected from:

N-(2-Amino-5-thiophen-2-yl-phenyl)-4-((*S*)-fluoro-methylcarbamoyl-methyl)-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-((*R*)-fluoro-methylcarbamoyl-methyl)-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[(1*R*)-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-[(1*S*)-fluoro-2-(4-methyl-piperazin-1-yl)-2-oxo-ethyl]-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-(*S*)-fluoro-methyl)-benzamide;
N-(2-Amino-5-thiophen-2-yl-phenyl)-4-(carbamoyl-(*R*)-fluoro-methyl)-benzamide;

or a pharmaceutically acceptable salt or stereoisomer thereof.

11. A pharmaceutical composition comprising a pharmaceutically effective amount of the compound of any of claims 1-10, and a pharmaceutically acceptable carrier.

12. The use of the compound according to any one of Claims 1 to 10 for the preparation of a medicament useful in the treatment or prevention of cancer in a mammal.